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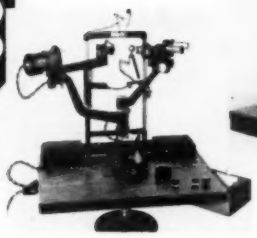

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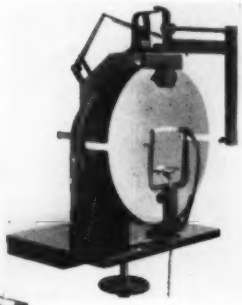

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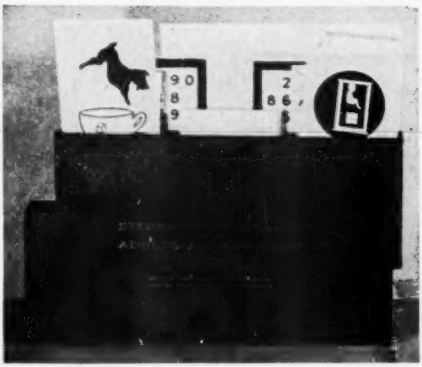

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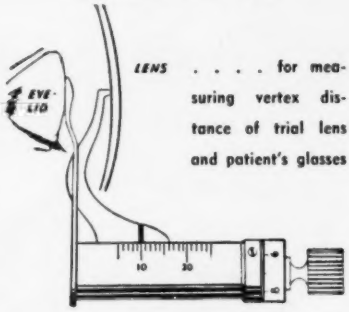

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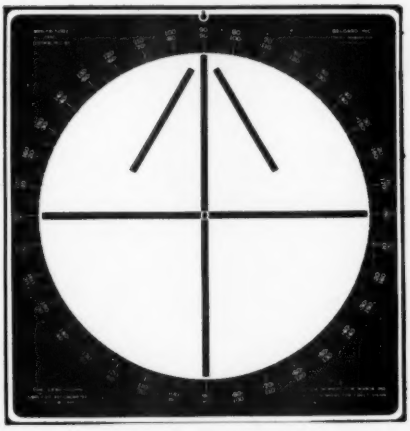

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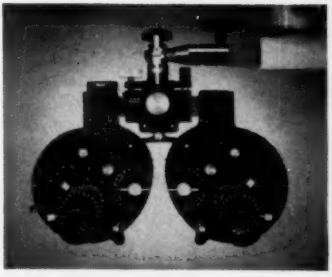

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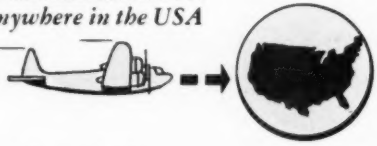

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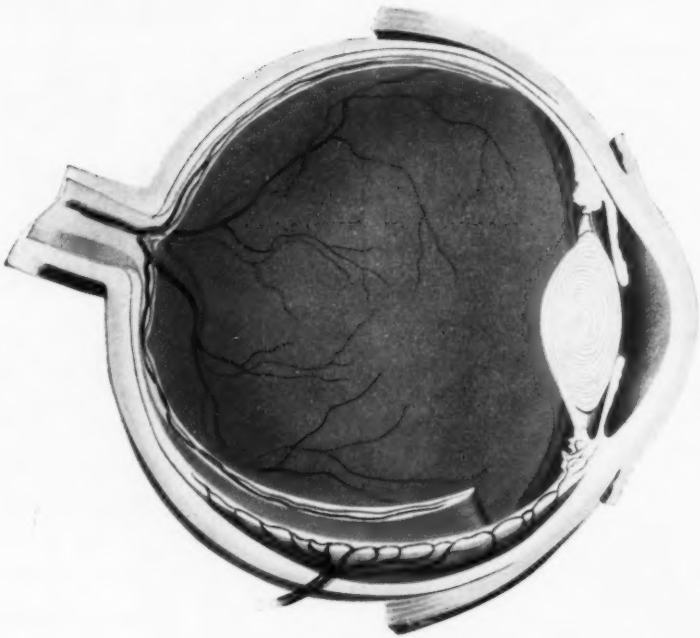

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1. Bland, T., et al: *Antibiotics & Chemotherapy* 1:753 (July) 1951.
2. Bland, T., and Tanabe, C.: *Antibiotics & Chemotherapy* 1:1145 (Nov.) 1951.

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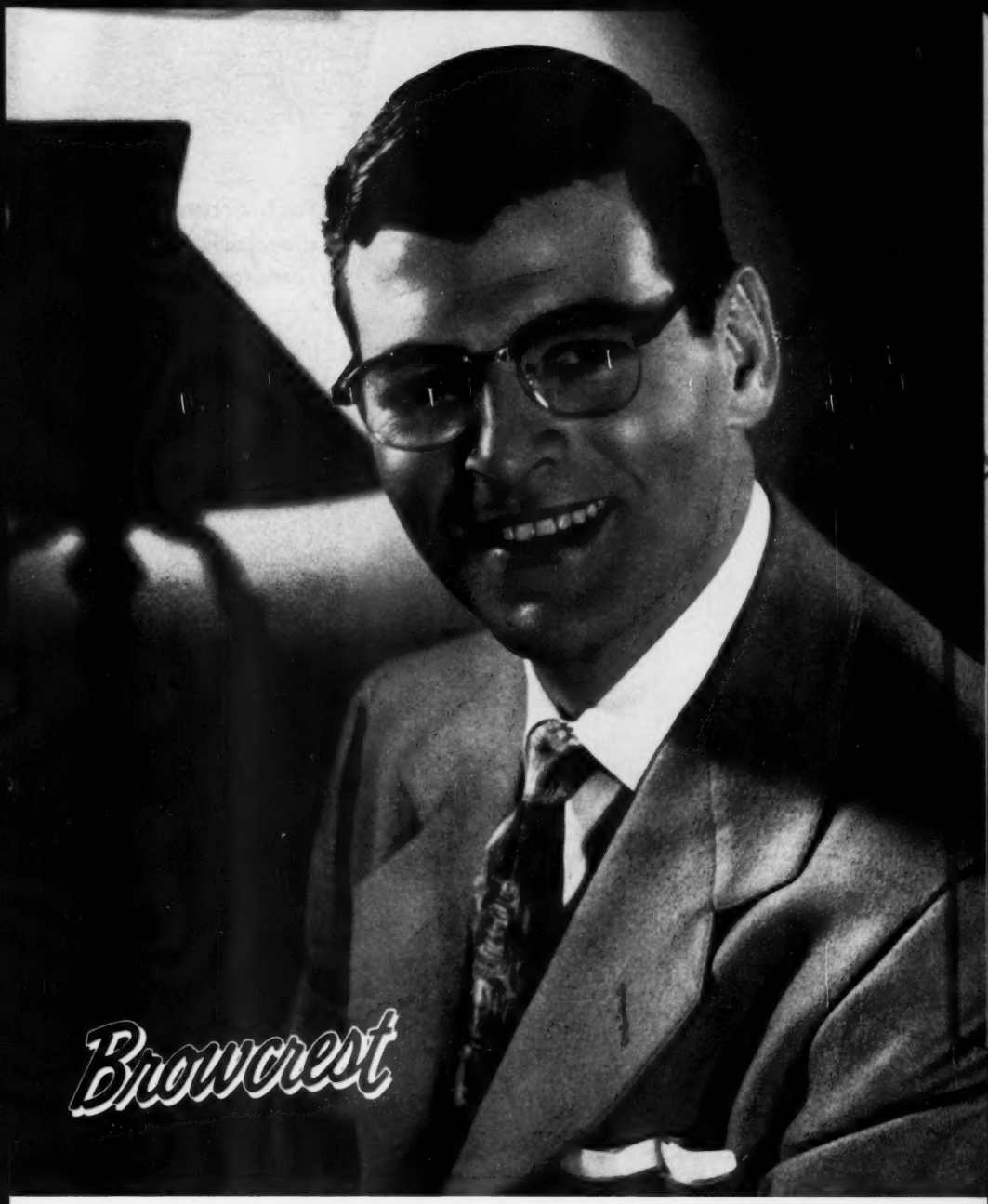

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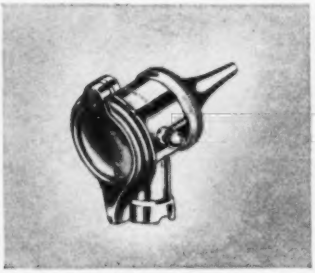

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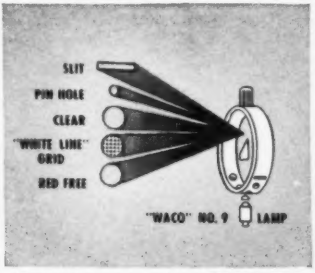

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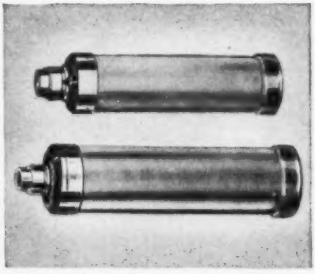

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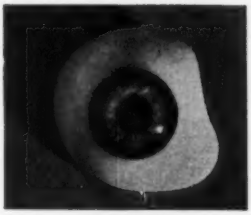

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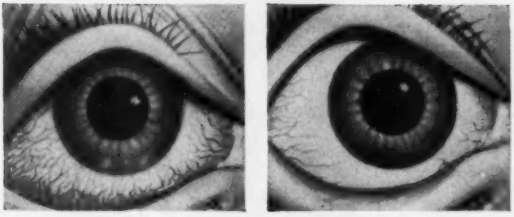

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1. Scheie, H. G., Tyner, G. S., Buesseler, J. A., and Alfano, J. E., *J. A. M. A. Arch. Ophth.* 45:301, March 1951.

2. Leopold, I. H., Purnell, J. E., Cannon, E. J., Steinmetz, C. G., and McDonald, P. R., *Am. J. Ophth.* 34:361, March 1951.

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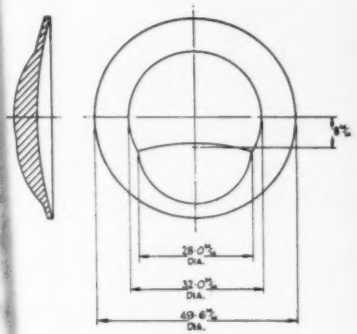

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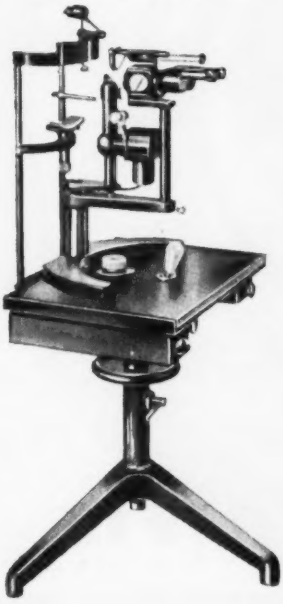

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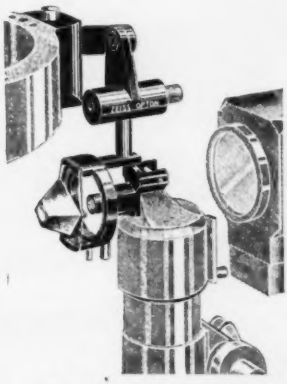

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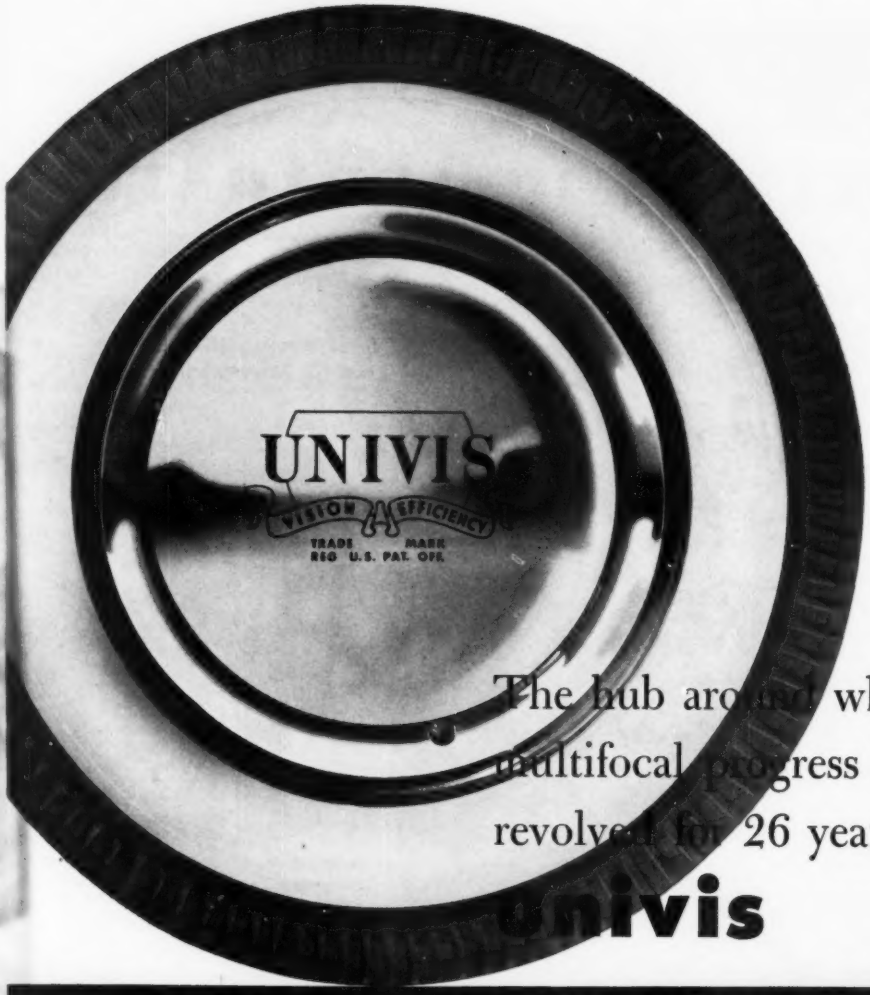

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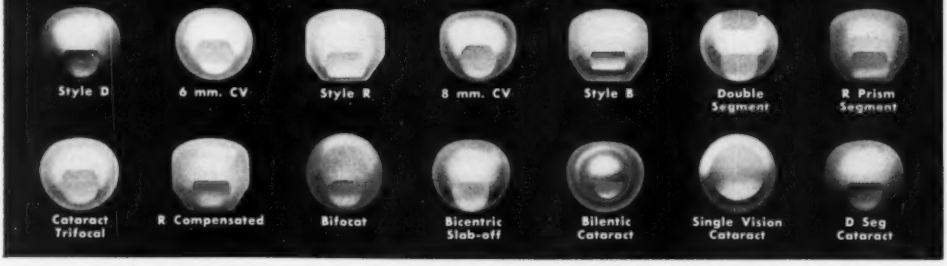

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ASSOCIATION OF UVEAL NEVI WITH SKIN NEVI

ALGERNON B. REESE, M.D.
NEW YORK

THE WORD nevus is derived from *natus* ("born") and was originally used loosely to designate almost any type of the so-called birthmark. It is still applied rather ambiguously to various unrelated conditions, principally to pigmented lesions of the skin and mucous membranes, but also commonly to certain types of hemangioma (naevus flammeus and port-wine hemangioma of the skin) and sometimes to various pigmented tumors of the uveal tract. It is now generally believed that the term should be restricted to lesions composed of so-called nevus cells. The nevus cell is a ubiquitous component, with definite characteristics; but its precise nature has been the subject of extensive controversy. The argument has been raging, indeed, virtually from the birth of the cellular concept, and only in recent years have there been any areas of agreement among observers. At the present most pathologists accept the Masson theory that nevus cells are modified Schwann cells—abortive attempts to form sensory end-organs, and to be found, therefore, at the sensory nerve terminals. Although nevi have generally been regarded as occurring in contiguity with the skin or a mucous membrane, it is now appreciated that nevus cells may be found almost anywhere over the body.

In ophthalmology we are familiar with nevi of the conjunctiva and of the skin of the lid. More recently we have become conscious of them as not uncommon lesions of the iris and ciliary body.[1] These uveal nevi seem to have no clinical characteristics to distinguish them from other pigmented lesions, e. g., the ordinary Schwannian melanoma or the stromal melanoma; but in my experience they have been found most frequently in the periphery of the iris, have displayed a coherent structure, so that usually there are no desquamated tumor cells or implantation growths to be seen, and have been well localized. Although relatively benign, they are capable of sudden, rather rapid acceleration of growth.

If we accept the Masson postulate that nevi occur at sensory nerve terminals, the iris and ciliary body would be likely sites of localization and the choroid an unlikely site. A choroidal nevus must indeed be an extreme rarity; but, although I have never recognized histologically a nevus cell in a choroidal lesion, such a lesion which may have been a nevus has come to my attention and will be described in this report.

From the Institute of Ophthalmology, Presbyterian Hospital.

Read at the Eighty-Seventh Annual Meeting of the American Ophthalmological Society, White Sulphur Springs, W. Va., June 7, 1951.

1. Wilder, H. C.: Intraocular Tumors in Soldiers, World War II, Mil. Surgeon, **99**:459, 1946.

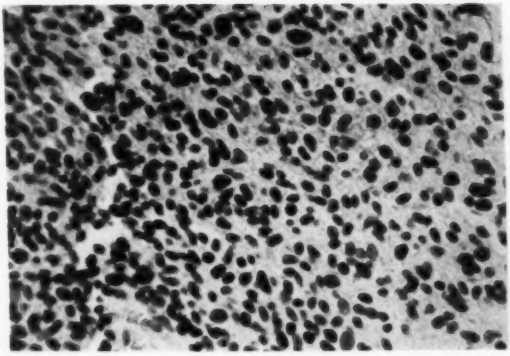
The purpose of this paper is to point out the not infrequent association of iris nevi with ipsilateral skin nevi. I have seen this association a sufficient number of times to feel that it is not accidental and that it may sometimes be clinically useful in indicating the true nature of a pigmented lesion of the iris. The following cases are illustrative.

REPORT OF CASES

CASE 1 (Figs. 1 and 3*A*).—P. M.,[2] a woman aged 21, had had a pigmented spot on the iris of the left eye since early infancy. Recently there had been an increase in its size, and medical

A

B



C

D

Fig. 1 (Case 1).—*A*, the skin nevi over the left side of the face.

B, the excised tumor. The base is relatively benign and is avascular, while the expanded portion shows malignant changes and is highly vascular.

C, structure of the tumor at a site between the base and the expanded portion, showing nevus cells and early malignant changes.

D, nevus cells in the base of the tumor. Two of the nuclei show vacuolations characteristic of nevus cells.

advice had been sought because of blurred vision. On examination this was found to be due to a hemorrhage in the anterior chamber of the left eye, and there was noted in the iris of the left eye a pyramidal mass protruding into the anterior chamber from the angle between 4 and 5

2. A patient of Dr. John W. Burke.

o'clock. The hemorrhage had evidently come from the large vessels in the tumor and had absorbed quickly. The broad base of the lesion was somewhat brownish and contained a few blood vessels. The apex of the mass was nonpigmented, flesh-colored, translucent due to cystic spaces, and highly vascular. Over the surface of the central, protruding portion there were three foci which represented either hemorrhage in the superficial layers or tremendously dilated vessels. It was thought that the apical portion represented recent, active growth arising from the older, basal portion. Gonioscopic examination revealed no desquamated cells or implantation growths in the angle or over the surface of the iris. The growth seemed to be well localized. In the periphery of the iris large, nutrient vessels coursed toward the lesion.

The patient had many pigmented spots over the body, and a year before the present examination one of these had been removed from the left shoulder because it had increased in size. There were many nevi on the face, most of them (seven) on the left side; the largest measured 4 by 3 mm. On the right side there was one under the angle of the jaw.

In view of the absence of desquamated tumor cells and the probability that the tumor did not extend to the extreme periphery of the iris, a local excision was performed by Dr. Burke.[2] The pathologic report stated that the lesion represented a malignant melanoma of the iris which

Fig. 2 (Case 2).—Location of the skin nevi over the left side of the head and neck. All had been excised.

had arisen from a nevus. There has been no evidence of recurrence to date, one year eight months after the excision.

CASE 2 (Figs. 2 and 3*B*).—H. B.,[3] a woman aged 40, had been aware of a pigmented spot on the iris of the left eye ever since she could remember. The question had now arisen as to whether or not this lesion had become larger. Examination showed in the left iris, temporally and above, an elevated, rather sharply demarcated, pigmented lesion with only a few small blood vessels visible over its surface. With the gonioscope, some pigment dust could be seen in the angle below, but the iris in the periphery beyond the tumor appeared to be normal. There were two pigment freckles on the left iris below; none was present on the right iris.

The patient had many skin nevi over the body and stated that a number of others had been removed from the face—one from under the left brow (a large one, with hairs over its surface), another from the left brow, and still another from the left side of the chin.

The iris tumor was excised, and microscopic examination showed it to be a nevus with possible early malignant changes. There has been no evidence of recurrence in the 15 months since the excision.

3. Patient of Dr. Michael S. Brody.

CASE 3.—P. P.,[4] a man aged 51, had a pigmented tumor in the periphery of the iris of the left eye between 8 and 10 o'clock. This elevated, rather well-localized lesion showed, with the gonioscope, some extension of the pigmentation into the immediately adjacent stroma, and some pigment dust along the posterior surface of the cornea opposite. No disseminated cells could be seen in the angle. There was one pigment freckle on the surface of the iris near the lesion.

In the periphery of the right fundus there was a benign melanoma, between 10 and 11 o'clock.

The patient had had a large brown mole, or nevus, excised from the left side of the nose.

CASE 4.—L. B.,[5] a woman aged 39, had an elevated, pigmented tumor in the periphery of the left iris, in the lower outer quadrant. With the gonioscope, ramifactions of the tumor cells could be seen in the adjacent iris stroma, but there were no disseminated tumor cells in the angle. On the left side of the forehead there was a pedunculated, slightly pigmented nevus, or perhaps a neurofibroma, measuring 5 mm. in diameter.

In these four cases elevated, rather well-localized, pigmented tumors occurred in the periphery of the iris in association with skin nevi predominantly on the same side of the face. In two cases questioning elicited a history of the former existence of other skin nevi which had been excised because they were unsightly. In two cases there were iris freckles on the affected iris and none on the fellow iris, and in one case the ipsilateral skin lesion bore clinical resemblance to a neurofibroma.

Two additional cases have been seen in which there were a melanoma of the iris, comparable to those described above, in one eye and a large, elevated nevus on the margin of the lower lid of the fellow eye.

As previously stated, a choroidal lesion suggestive of a nevus has been observed. A boy aged 7½ years had a large pigmented nevus over the left side of the head, particularly over the temporal region but involving also the skin of the upper and lower lids (Fig. 3*C*). In the fundus of the left eye there was an unusual lesion, elevated and nonpigmented, temporal to the optic disk (Fig. 3*D*). Although no microscopic verification was possible, this lesion could have been a nevus, or possibly a neurofibroma, of the choroid.

COMMENT

There is a close relationship between the nevus and the neurofibroma. The nevus, if one accepts the Masson theory, is composed of modified Schwann cells and represents an abortive attempt to form sensory end-organs; the neurofibroma is composed of unmodified Schwann cells. There are instances in which both the nevus cell and the Schwann cell, and all gradations between, have occurred in the same lesion (dermal nevus). In the cases described in this report skin nevi predominated. Only in Case 4 was the skin lesion apparently a neurofibroma, and its identity could not be established microscopically. The association of a neurofibroma, or of neurofibromatosis, with uveal melanomas has been reported by Goldstein and Wexler,[6] Bair and Love,[7] Gartner,[8] and Strakhov.[9] In Strakhov's case there was also a neurinoma of the orbit.

4. A patient of Dr. Francis H. Adler and Dr. Irwin Levy.

5. A patient of Dr. Girolamo Bonaccolto.

6. Goldstein, I., and Wexler, D.: Melanosis Uveae and Melanoma of the Iris in Neurofibromatosis (Recklinghausen), Arch. Ophth. **3**:288 (March) 1930.

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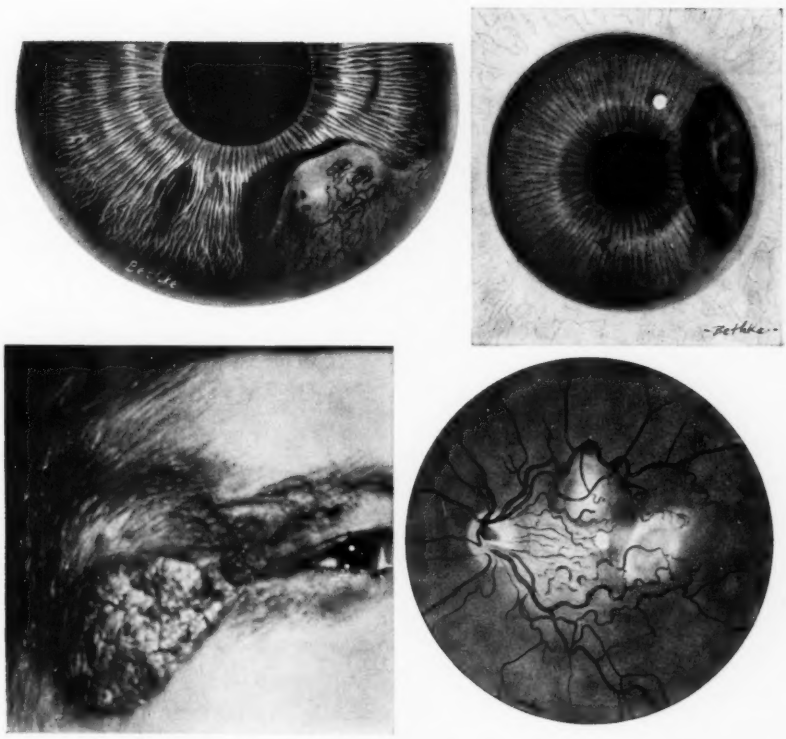

Fig. 3.—Upper left (Case 1), clinical appearance of the tumor of the left iris.

Upper right (Case 2), clinical appearance of the tumor of the left iris. There are also three iris freckles. None was present on the fellow iris.

Lower left, an extensive pigmented nevus in the left temporal region, as well as on the upper and lower lids.

Lower right, the left fundus of the patient whose skin nevus is shown in *C*, with a lesion temporal to the disk, which is supposedly related to the skin nevus.

As compared with other pigmented lesions, the true nevus represents a relatively common type of melanoma of the iris. When a pigmented lesion of the iris is associated with excessively numerous or large ipsilateral skin nevi, it is likely to be a nevus. Although the majority of such lesions will, in all probability, never become malignant (Cases 2, 3, and 4 are probably of this order), there is always the possibility that the iris nevus will take on active growth (Case 1) and, in my opinion, is much more likely to become malignant than is the skin nevus. For this reason, it may be advisable as a general rule to excise all nevi of the iris. If it is possible to observe the lesion at frequent intervals for evidence of active growth, excision may be deferred until such evidence has developed. Frequent observation, however, may so alarm the patient that an excision will have to be performed to relieve him of his apprehension. Complete local excision of the iris nevus is possible in most cases because the lesion is localized, usually does not extend to the periphery of the iris, and does not give rise to disseminated tumor cells or implantation growths. It is true that with the gonioscope pigment dust is sometimes seen in the angle, but I do not believe that this necessarily represents cast-off tumor cells capable of autogenous growth.

Callender, Wilder, and Ash [10] report that the Registry of Ophthalmic Pathology has recorded 3 deaths in 32 cases of malignant melanoma of the iris, or a mortality of only 9.4%. Three of the patients on whom an iridectomy alone was performed were living and well seven years later. A factor in the comparatively low mortality in these cases may be the relatively early detection of this type of tumor, and it is my belief that a further factor may very well be the high incidence of nevi among melanomas of the iris.

SUMMARY AND CONCLUSION

Four cases are described in which elevated, rather well-localized, pigmented tumors occurred in the periphery of the iris in association with skin nevi predominantly on the same side of the face.

In two of the four cases there were freckles on the affected iris and none on the fellow iris.

In two additional cases a nevus-like melanoma of the iris was associated with a nevus of the margin of the lower lid of the fellow eye.

One choroidal lesion which may have been a nevus was observed in association with an extensive ipsilateral pigmented nevus of the skin of the head and eyelids.

These observations suggest that when a pigmented lesion of the iris is associated with excessively numerous or large ipsilateral skin nevi it is likely to be a nevus.

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FURTHER EFFORTS TO INFLUENCE X-RAY CATARACT BY CHEMICAL AGENTS

LUDWIG VON SALLMANN, M.D.
With the Technical Assistance of Carmen M. Munoz
NEW YORK

ACCORDING to the target theory, significant radiobiological effects are produced solely by direct hits of single ionizing particles upon sensitive parts of irradiated cells. During the past 10 years, however, studies on the effect of x-rays on aqueous solutions of various chemical substances have indicated that indirect biochemical mechanisms mediate at least some of the actions of ionizing radiations. Of these biochemical processes, the production of active radicals by the ionization of water is best understood and is believed to be of first importance, although such other possibilities as the shifting of the redox potential of critical areas and the depression of metabolic processes by irradiation have been suggested. In vitro investigations on solutions of highly polymerized desoxyribonucleic acid [1] and on sulfhydryl enzymes [2] have shown clearly that the effectiveness of the radiation is decreased in the presence of other solutes, i. e., that chemical agents can protect irradiated compounds against x-ray effects. Similar studies have been extended

This study was supported by the Knapp Memorial Foundation.

Read in part at the Eighty-Seventh Annual Meeting of the American Ophthalmological Society, White Sulphur Springs, W. Va., June, 1951.

From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

The studies on the effect of x-rays on the lens, of which this paper is a part, are based on work performed under Contract #AT-30-1-Gen-70 of the Atomic Energy Commission.

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by other workers to such biological material as bacteria [3] and small laboratory animals.[4] The relative protection of these living systems against x-ray damage by the introduction of chemicals in excess suggests the inadequacy of the target theory as originally proposed.

The beneficial influence of — SH-containing substances in reducing the effect of total body irradiation of rats and mice was demonstrated by the achievement of a higher survival rate among animals pretreated with thiols (cysteine,[4f-i] glutathione,[3b] thiourea [4i]) than among control animals which had been exposed to the same lethal dose of x-rays. However, owing to the complexity of factors involved in these experiments, the chemically induced lower mortality of experimental animals after exposure to a relatively high dose of x-rays gives no clear indication of the usefulness of pretreatment with such agents for reducing the sensitivity of ocular tissues to locally applied ionizing radiations.

Last year, in a preliminary study, my co-workers and I [5] reported on the relation of treatment with cysteine to the x-ray damage of rabbit eyes which had been exposed to a single dose of 1,500 r of penetrating x-rays. It was concluded that the usual signs of radiation damage in the region of the eye, such as keratoconjunctivitis, transient iritic changes, and pigment proliferation from the limbus into the cornea, were not influenced greatly by pretreatment of the animals with this

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amino acid. On the other hand, complete epilation of the exposed lids, which regularly takes place as a result of this dose of x-rays, was prevented by intravenous injection of cysteine (2 gm. per animal) prior to the irradiation. It was shown, moreover, that the onset of radiation cataract could at least be greatly delayed if the eyes were not rayed until from 5 to 30 minutes had elapsed after the use of the chemical compound.

The present study was divided into three parts. First, it had to be shown by prolonged observations whether the reported early beneficial effect of cysteine treatment on x-ray damage of the lens was of transient or relatively permanent character, and whether it could be influenced by additional use of the amino acid at later periods. The effect of lower concentrations of cysteine in the aqueous humor, obtained by local use of the compound, was evaluated in this connection. Second, the development of microscopic signs of x-ray damage to the lens was analyzed in eyes rayed before and after the intravenous use of cysteine. This included the recording of early nuclear and cytoplasmic changes, both structural and cytochemical, and of the effect of the radiation on the mitotic activity of the lens epithelium under the conditions of the experiments. Finally, investigations were carried out on the influence of thiols other than cysteine, of compounds classified as reductants or antioxidants which did not contain — SH groups, of a substance known as citrovorum factor, which supposedly protects certain phases of mitotic activity, and of a metabolic poison.

LATE EFFECTS OF TREATMENT WITH CYSTEINE PRIOR TO LOCAL IRRADIATION OF THE RABBIT EYE WITH 1,500 R

Materials and Methods.—The experimental animal used throughout the study was the mature chinchilla rabbit. The technique of separate irradiation of the right and left eyes, with the unrayed, shielded eye outside the beam, was described in a previous report. In the present series of experiments, 1,500 r (220 kv.; 20 ma., 145 r per minute; 0.5 mm. Cu 1 mm. Al filtration; 30 cm. target-skin distance; 20-mm. field, "round") was given in one session.

A large series of rabbits received 2 gm. of *l*-cysteine base intravenously shortly after irradiation of the right eyes and 30 minutes before irradiation of the left eyes. Fourteen of these rabbits were observed for more than a year. Measurements with an ionization chamber in the orbit of the nonirradiated side of control animals showed that the nonirradiated globes may have been exposed to 5 r of stray radiation.

Since other experimental radiobiological studies indicated that environmental factors can influence the radiation effect when introduced after the exposure of biological material to x-rays, the left eyes of six additional rabbits, which had received systemic injections of cysteine before the exposure of both eyes to 1,500 r, were given subconjunctival injections of 0.5 cc. of an 8% solution of cysteine base at three-day intervals for three weeks after irradiation. Only four of the six rabbits could be used for late observations. In another series, of 14 animals, subconjunctival injection of 1 cc. of an 8% solution of cysteine in the left eye preceded the exposure to the x-ray beam by 30 minutes.

The animals in which there was a difference in the development of radiation damage between the right and the left eye were observed at intervals for periods up to 16 months by the routine methods of ophthalmoscopy and biomicroscopy, with maximal dilation of the pupil. In the study already reported, levels of cysteine and cystine in the aqueous humor were measured at various time intervals after administration of the drugs by various routes. There was no need to repeat these measurements.

Results.—Of the rabbits treated with cysteine by the intravenous route alone, only those are mentioned here which were kept under observation for over one year. The previously reported epilation on the right side appeared to be permanent and to have been prevented on the left side by the use of cysteine prior to irradiation.

In 13 of the 14 animals total cataract had formed in from 3½ to 18 months after irradiation in the eyes which were rayed before the systemic use of cysteine. The remaining animal of the group showed advanced, but partial, lens opacities on the right side 18 months after the x-ray treatment. At this time no opacity which was dense or extensive enough to interfere substantially with the visibility of fundus details had developed in any of the eyes of the rabbits which had been irradiated after cysteine was introduced. All these lenses showed opacities, however, mostly of a fine ring or star shape, in the posterior pole, which were sometimes combined with delicate lesions in the anterior cortex (Fig. 1). As far as can be judged at the time of writing, about 18 months after irradiation, these opacities seem to be stationary and to resemble the well-known picture of early x-ray or radium cataract in the human eye. The time of onset of the lens changes in these eyes was several months later than it was in the control eyes (Table 1).

In the four animals in which the left eyes were given local cysteine treatment for three weeks after both eyes had been irradiated with 1,500 r subsequent to intravenous injection of cysteine epilation was absent or very slight on both sides after

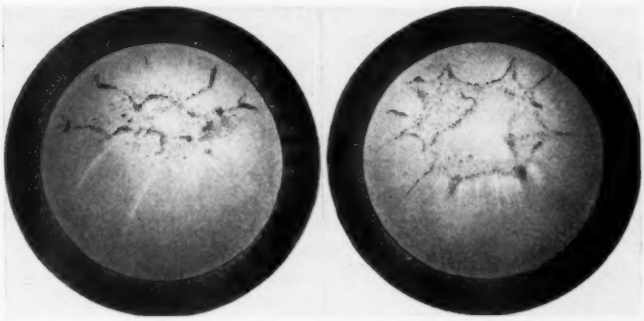

Fig. 1.—Opacities of the posterior cortex in cysteine-protected lenses one year after irradiation.

five months, and the initial lens opacities at the equator showed the same intensity and extent in the right and in the left eyes after six months. Thus, the protracted local treatment with cysteine apparently did not influence the course of the mild x-ray damage in the lenses of eyes which had been irradiated after the use of cysteine by intravenous injection (Table 1).

In the last group of experiments, in which the effect of local treatment was studied, the right eyes of 14 rabbits received 1 cc. of an 8% solution of cysteine subconjunctivally prior to irradiation. Four animals had to be discarded because of disease. In the remaining 10 animals there was little evidence that the cysteine treatment exerted a deterrent effect on epilation other than to delay it slightly (about one week). On the other hand, in the eyes which had received injections of cysteine, the equatorial granular-ring opacity in the lens showed up several weeks later than in the control eyes. As yet, total cataract has developed in only two eyes of the control group and in none of the cysteine-pretreated eyes, but the observation period has not exceeded nine months. With reference to the moderate, and occasionally questionable, effect of the local use of cysteine on radiation damage of the lens, it

should be remembered from a former study [5] that the cysteine-cystine level in the aqueous humor after this type of administration is about one-fourth that obtained by intravenous use of the compound.

Comment.—The preliminary conclusions of the previous paper,[5] to the effect that cysteine induced relative radioresistance of the lens and hair follicles to local exposure of the rabbit eye to 1,500 r, were confirmed by prolonged observation of the animals so treated. If it were permissible to evaluate observation periods of pathological events as fractions of the life span of a species, one year in the rabbit's life would correspond to a period of from 10 to 15 years in the human life, and it could be said that the fine lenticular opacities in the cysteine-protected irradiated eyes presented a rather stationary type of partial radiation damage, a damage slight indeed if one considers the magnitude of the dose of x-rays.

TABLE 1.—*Onset of X-Ray-Induced Cataractous Changes in Eyes Receiving One Dose of 1,500 r Before and After Cysteine Treatment*

Time After Irradiation	Cysteine Treatment	No. of Lenses in Which Developed					
		Posterior Cortical Opacity		Anterior Cortical Opacity		Total Cataract	
		O. D.	O. S.	O. D.	O. S.	O. D.	O. S.
4-6 wk.	2 gm. I. V. ½ hr. prior to irradiation of O. S.*	6	..	1	..	..	..
7-9 wk.		6	..	3	..	..	..
10-12 wk.		2	1	8	3	..	..
3½ to 5 mo.	.....	..	8	2	7	5	..
6-8 mo.	.....	..	5	..	3	4	..
9-18 mo.	.....	..	..	..	..	4	..
4 wk.	80 mg. subconjunctivally ½ hr. prior to irradiation of O. S.	1	..	..	..	..	..
6-8 wk.		6	2	..	..	..	..
3-5 mo.		3	3	5	4	1	..
6-8 mo.	.....	..	1	2	1	..	..
10 mo.	.....	..	..	..	..	1	..
4 mo.	2 gm. I. V. ½ hr. prior to irrad. of O. U.†	..	..	2	2	..	..
5 mo.	O. S.: 6 subconjunctival inj. during 3 wk. after irrad.	2	2	2	2	..	..
8 mo.		2	2	..	..	..	..

* Right eye irradiated prior to cysteine treatment and nonprotected.
† Both eyes protected with cysteine injected intravenously; left eye had additional treatment subconjunctivally after irradiation.

The demonstration of the protection phenomenon in connection with such late injurious x-ray effects as radiation cataract supplements what has already been observed of the effect of cysteine pretreatment on the more acute and more complex x-ray action which follows total body irradiation with a lethal dose. Patt and co-workers [4f-i] have provided significant data on the protective influence of such treatment against x-ray deaths in rats. They analyzed their results also from the viewpoint of the relative timing of the two procedures and with reference to the dependence of the protection upon the quantity of employed — SH compounds. The necessity of having comparatively high levels of the reduced form of the amino acid distributed in the tissue before the exposure to x-rays was shown also in the present study on the eyes, in which information on the cysteine-cystine ratio could be supplied for the blood and aqueous humor by the determination of the — SH and — SS groups.

As to the influence of cysteine protection on x-ray epilation, it was shown in the present series that the initially observed results were permanent. A study of

Forssberg, published at the time the early observations of this laboratory were reported, dealt with the favorable effect of local cysteine treatment on circumscribed areas of the guinea pig's skin when the medication preceded irradiation with not more than 950 r of a softer fraction of the x-ray spectrum than was used in our series on rabbits.

The failure of a single administration of a high dose of cysteine, given immediately after completion of irradition, to inhibit epilation and the formation of x-ray cataract, did not exclude the possibility that prolonged cysteine therapy, within the weeks in which the microscopic signs of radiation damage were beginning to develop, might have a deterrent effect. The investigations of Packard,[6] Wood and Prime,[7] Strangeways and Fell,[8] and others indicated that environmental factors introduced after irradiation could have an important influence on the effect of x-rays on biological material. In the same vein, a prolongation of survival times among irradiated mice was recorded by Goldfeder and co-workers [4c] when folic acid and pyridoxine hydrochloride were administered not only before irradiation, but for several weeks thereafter. In contrast to these findings, the combination of pretreatment of rayed rabbits with intravenously administered cysteine and of post-treatment use of the compound in the form of subconjunctival injections for three weeks did not seem to alter the appearance of the fine lenticular opacities which were observed in the eyes protected by cysteine pretreatment alone.

It was determined in the earlier study [5] that levels of about 10 mg. of cysteine and cystine per 100 cc. were present in the aqueous humor 30 minutes after subconjunctival injection of 0.5 cc. of an 8% solution of cysteine base. The ratio of the reduced form of the amino acid to the oxidized form was slightly above 1. A comparison of the partially favorable results of this form of treatment and the completely negative results of intraperitoneal administration suggested that the partial protection in the first instance was connected with this ratio rather than with the absolute amount of cysteine in the aqueous humor. In the present series the limited protective effect of pretreatment of the rabbit with subconjunctival injections of cysteine was considered moderate when compared with the results observed after intravenous injections, but since the dose of 1,500 r exceeded by between three and four times the cataractogenic dose in this experimental animal,[9] this modestly beneficial influence may have practical significance.

EARLY STRUCTURAL AND CYTOCHEMICAL CHANGES OF TISSUE ELEMENTS OF THE LENS AND ALTERATIONS IN THE MITOTIC INDEX OF THE LENS EPITHELIUM INDUCED BY X-IRRADIATION IN RABBITS TREATED WITH CYSTEINE

The experiments of this part of the study were concerned solely with the intravenous use of cysteine base because of the striking effect of this treatment in the partial prevention of x-ray cataract.

6. Packard, C.: Relation Between Division Rate and Radiosensitivity of Cells, J. Cancer Res. **14**:359, 1930.

7. Wood, F. C., and Prime, F.: Action of Radium on Transplanted Tumors of Animals, Ann. Surg. **62**:751, 1915.

8. Strangeways, T. S. P., and Fell, H. B.: A Study of the Direct and Indirect Action of X-Rays upon the Tissues of the Embryonic Fowl, Proc. Roy. Soc., London, s.B **102**:9, 1927.

9. Cogan, D. G., and Donaldson, D. D.: Experimental Radiation Cataracts: I. Cataracts in the Rabbit Following Single X-Ray Exposure, A. M. A. Arch. Ophth. **45**:508, 1951.

Materials and Methods.—The technique of irradiation and of cysteine treatment and the relative timing of the two procedures were the same as those used in the experiments of the first section of the study. The animals were killed in from two hours to three weeks after the exposure to 1,500 r, and more than 100 eyes were subjected to microscopic examination. The lenses of the freshly killed rabbits were fixed in Carnoy solution during the process of removal and were dissected in such a way as to obtain 5-μ meridional sections with the paraffin technique. The various steps of preparing the material have been described in another paper.[10] The Feulgen reaction and the methyl-green technique were used again for cytochemical analysis of changes in the content of desoxyribonucleic acid in the cell nuclei.

A new method devised by Dr. A. Howard[11] of London, England, was employed for flat preparations of the entire lens epithelium. It consisted in fixing the anterior portion of the equatorially bisected globes immediately in Carnoy solution for 24 hours, and in passing these preparations through 70% alcohol for an additional 24 hours and then through water for ½ hour. Hydrolysis in normal hydrochloric acid and staining in the Feulgen reagent for one hour were carried out on the intact lens after it had been freed by gentle pressure on the cornea from its connection with the zonular fibers. The sharp posterior demarcation of the lens epithelium at the equator was indicated by an intense red line. After a quick rinse in water, the capsule was circumcised behind this landmark and the preparation transferred to the bleaching solution. With the lens suspended in this fluid, the anterior half of the capsule with the epithelium was separated from the bulk by gentle pushing with a fine eye spatula and by rotation of the lens in the fluid. The isolated capsule with epithelium was spread in a drop of water on a cover slip with the epithelial layer toward the surface of the glass, was radially incised and stretched where necessary, and finally mounted on a slide in chrome-gelatin. This kind of flat preparation of the epithelium was well suited to high-power microscopy and the determination of the mitotic activity in this cell layer; it was not suitable for an evaluation of changes in the lens bow or the lens fibers or for the estimation of cytochemical reactions. The latter purposes were well served by the technique with thin meridional sections, which made possible a direct comparison of the experimental preparations and identically treated sections of control eyes.

Results.—In previous studies on the effect of x-rays on the lens, produced by 2,000 or 1,500 r, it was found that the earliest structural changes became visible in meridional sections about one week after irradiation. They consisted in (1) beginning fragmentation of chromatin, (2) swelling of the cytoplasm of some cells in the preequatorial area, and (3) displacement of individual nuclei of the lens bow back and forward. As a rule, a decrease in the content of desoxyribonucleic acid in many of the nuclei in the peripheral part of the epithelium was not noticed in the rayed eyes until three weeks had elapsed after irradiation, but it was suspected that the method of quantitation used in these experiments might not have been delicate enough to determine small differences.

The three cytologic changes were utilized in the present study to evaluate the protective influence of cysteine treatment prior to irradiation of the eye. Counts of the number of displaced nuclei in the lens bow were suitable for semiquantitative comparison of the radiation effects on the two eyes of the irradiated cysteine-treated rabbits. Table 2 shows that in the control eyes the change in the position of individual nuclei in this part of the lens occurred earlier and was more extensive during the first three weeks of observation. In thin sections the counts of the number of cells in the preequatorial zone (Table 3) indicated that destruction of cell

10. von Sallmann, L.: Experimental Studies on Early Lens Changes After Roentgen Irradiation: I. Morphological and Cytochemical Changes, A. M. A. Arch. Ophth. **45**:149 (Feb.) 1951.

11. Howard, A.: Personal communication to the author.

elements in this area in the control eyes was greater than it was in the eyes irradiated after cysteine had been given, but was the same as in irradiated eyes which had received no cysteine treatment whatever. Unexpected on clinical grounds was the observation in a later stage of radiation damage which showed that the development of interfibrillary and intrafibrillary vacuoles and the formation of cystic spaces at

TABLE 2.—*Number of Nuclei Displaced from the Bow of Rabbit Lenses, Irradiated with a Single Dose of 1,500 r Immediately Prior to and One-Half Hour After Intravenous Injection of 2 Gm. of Cysteine Base* *

Time After Irradiation, Wk.	No. of Rabbit Lenses	No. of Displaced Nuclei †	
		O. D.	O. S.
1	4	1. 2.8 2. 0.91	1. 1.17 2. 0.33
1-½	2	1. 2.6	1. 2.1
2	4	1. 0.28 2. 6.0	1. 0.12 2. 3.0
3	2	1. 2.0	1. 0.45
4	4	1. 1.54 2. 4.0	1. 0.37 2. 1.9
6	4	1. 15.3 2. 7.2	1. 12.0 2. 5.1

* Right eye irradiated prior to cysteine injection; left eye irradiated one-half hour after cysteine injection.
† Each figure is the average of counts for at least 10 sections of each lens.

TABLE 3.—*Cell Counts in Preequatorial Epithelium of Rabbit Lenses Irradiated with One Dose of 1,500 r Immediately Prior to and One-Half Hour After Intravenous Injection of 2 Gm. Cysteine Base* *

Time After Irradiation, Wk.	No. of Rabbit Lenses	Counts †	
		O. D.	O. S.
1	4	1. 87.0 2. 57.0	1. 92.0 2. 50.0
1-½	2	1. 54.6	1. 66.4
2	4	1. 64.6 2. 32.4	1. 75.2 2. 67.8
3	2	1. 53.7	1. 74.0
4	4	1. 59.4 2. 47.0	1. 75.9 2. 58.2
6	4	1. 51.7 2. 44.1	1. 58.5 2. 63.4

* Right eye irradiated prior to cysteine injection; left eye irradiated one-half hour after cysteine injection.
† Each figure is the average of counts for at least six sections of each lens.

the ends of the fibers did not differ in the two eyes of the cysteine-treated animals in the few experiments carried out in this phase.

As far as could be estimated by direct comparison of experimental and control eyes and by quantitation by means of Coujard slides,[12] the intensity of the Feulgen reaction appeared to be in the same range in eyes which had been exposed to x-rays after the use of cysteine as in eyes in which the irradiation preceded the use of cysteine. This finding was in line with the results of earlier studies carried out in this laboratory,[10] in which it was impossible to demonstrate the alleged early tran-

12. Gomori, G.: The Quantitative Determination of Histochemical Reactions for Enzymes, Exper. Cell. Res. **1**:34, 1950.

sient depression of the newly formed desoxyribonucleic acid [13] in irradiated tissue in sections through the lens epithelium after exposure of the eye to 2,000 r.

A great number of flat preparations were searched for finer structural lesions in the cells of the epithelium. At variance with previous observations recorded in our own series, and with those reported by Poppe,[14] the first lesions in the epithelial preparations could be identified as early as three days after irradiation, in the form of nuclear fragmentation and extrusion of Feulgen-positive material into the cytoplasm and then into the extracellular phase (Fig. 2). In the following days the accumulation of this material between the cells increased rapidly in the rayed eyes.

Investigations carried out by Poppe,[14] Cogan and Donaldson,[9] and in this laboratory [10] on early microscopically visible signs of radiation damage to the lens provided a basis for the study of the protection phenomenon. The results obtained

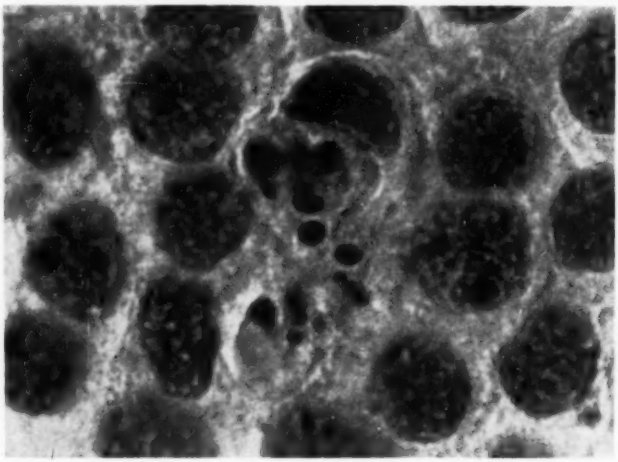

Fig. 2.—Nuclear fragmentation and extrusion of Feulgen-positive material into the cytoplasm and the extracellular phase.

on the control eyes in the present series corroborated to a great extent the results obtained by the other workers mentioned. However, no systematic investigation had been conducted on the mitotic activity of the lens epithelium under normal conditions or under the influence of the exposure to x-rays. It was first necessary, therefore, to provide data for establishing the mitotic index of the lens epithelium,

13. Stowell, R. E.: Effect of Roentgen Irradiation on Thymonucleic Acid Content of Transplantable Mammary Carcinomas, Cancer Res. **5**:169, 1945. Ahlstrom, L.; Euler, H., and Hevesy, G.: Über die kurzlebige durch Röntgenstrahlen bewirkte Hemmung der Nukleinsäurebildung, Arkiv kemi mineral. geol. **18**B(No. 13):1, 1944; Die Wirkung von Röntgenstrahlen auf den Nukleinsäureumsatz in der Organen der Ratte, ibid. **19**A(No. 9):1, 1945. Euler, H., and Hevesy, G.: Wirkung der Röntgenstrahlen auf den Umsatz der Nukleinsäure in Jensen-Sarcom II, ibid. **17**A(No. 30):1, 1944.

14. Poppe, E.: Experimental Investigations of the Effect of Roentgen Rays on the Epithelium of the Crystalline Lens, Acta radiol. **23**:354, 1942.

that is, the ratio of the number of dividing cells to the number of resting elements.[15] It was determined that the over-all mitotic index of the lens epithelium of the normal rabbit is approximately 27 : 100,000 and that this ratio varies greatly from zone to zone, being highest in the germinative area of the densely packed cells.

Complete inhibition of mitosis was present two hours after irradiation with 1,500 r of penetrating x-rays. From this time until three days after irradiation, dividing cells were completely absent in the lens epithelium except for a varying number of cells in early prophase. The level of the normal number of cells in mitosis in the rabbit lens epithelium—200 to 250 cells—was reached approximately one week after the local exposure of the eye to the beam of the rays. In the following weeks the counts of the dividing cells increased to about twice the normal figure. How long this phenomenon of overcompensation lasts has not yet been determined. The control eyes of rabbits which were not directly irradiated and were exposed to about 5 r of stray radiation did not show a depression of the mitotic activity.

In irradiated animals which had been pretreated with cysteine there seemed to be an inhibition of mitosis following irradiation which was as rapid as, but less complete than, that in rayed control animals, and a moderate delay in the processes of recovery and overcompensation. It would be unjustifiable, however, to draw definite conclusions from these differences until many more data from these laborious studies have been accumulated. Nor can the old controversy as to the most radiosensitive phase in the mitotic cycle be discussed at the present stage of our knowledge, although the results of preliminary work on about 80 eyes would indicate that the early prophase and interphase are the most sensitive for the ionizing radiation.

Comment.—The avascularity of the lens and the fact that it possesses a single layer of epithelial cells separated into two functionally different types, one of which produces the main bulk of fiber-shaped cytoplasm, provide conditions distinctly favorable for the evaluation of early radiation effects. Initial x-ray-induced changes in the nuclei and cytoplasm of these cells have been reported recently by several investigators.[16] On the basis of the knowledge thus provided, experiments were conducted in which comparable changes were induced in eyes which had been rayed before medication. It was thought possible to separate in this biological material the effects which were influenced by a chemical agent, and were therefore dependent on an indirect biochemical mechanism of radiobiological action, from other effects for which a different mechanism might be responsible. Certain morphological effects, e. g., the displacement of individual nuclei in the lens bow and the incidence of cell deaths in the preequatorial area, were less marked in the cysteine-pretreated eyes. According to Howard and Schultz,[17] early nuclear fragmentation can be considered an expression of the effort of the cell to preserve the nucleus-cytoplasm relationship. Friedenwald, Buschke, and Moses [18] have reported nuclear fragmenta-

15. von Sallmann, L.: Experimental Studies on Early Lens Changes After Roentgen Irradiation: III. Effect of X-Radiation on Mitotic Activity and Nuclear Fragmentation of Lens Epithelium in Normal and Cysteine-Treated Rabbits, A. M. A. Arch. Ophth. **47**:305, 1952.

16. Cogan and Donaldson.[9] von Sallmann.[10] Poppe.[14]

17. Howard, W. T., and Schultz, O. T.: Studies in the Biology of Tumor Cells, Monograph 2, Rockefeller Institute for Medical Research, 1911.

18. Friedenwald, J.; Buschke, W., and Moses, S.: XVI: Comparison of the Effects of Mustard, Ultraviolet, and X-Radiation, and Colchicine on the Cornea, Bull. Johns Hopkins Hosp. **82**:312, 1948.

tion in the basal layers of the corneal epithelium of rats after exposure to various doses of ultraviolet radiation or after the use of nitrogen mustard (methyl-bis- or methyl-tris-[2-chloroethyl] amine), but not after exposure to x-rays. In the present study of preparations from cysteine-treated rabbits, the extrusion of intensely stained material was observed earlier and more frequently in the control eyes, which were treated before the use of cysteine, than in the cysteine-protected eyes. The turnover of desoxyribonucleic acid was not noticeably influenced by the chemical agent; this is in contrast to observations by Limperos and Mosher,[41] who found that thiourea injected into rats before irradiation did inhibit to some extent the depolymerization of desoxyribonucleic acid in the thymus.

It is known that mitosis is one of the earliest cell functions affected by ionizing radiations and that the mitotic index is frequently used to express radiation damage. The introduction of cysteine did not alter greatly the temporary suppression of cell division by irradiation with 1,500 r, which lasted from two hours to three days after exposure to radiation, nor did it influence decisively recovery from the mitotic inhibition or the compensatory increase in the proportion of dividing cells during the second week after irradiation. Further experiments are planned on irradiation with lower doses, and with threshold doses which arrest mitosis.

It can be concluded, then, that most x-ray-induced early changes in the rabbit lens which could be studied microscopically were moderately influenced by the protective action of cysteine. An indirect biochemical mechanism of x-ray action must be responsible, at least in part, for eliciting these lesions. Since early transitory suppression in the turnover of desoxyribonucleic acid could not be demonstrated in the lens epithelium of nonmedicated animals, it was not surprising that no difference in the cytochemical reaction could be shown between eyes protected with cysteine and control eyes. The transient appearance of large cystic spaces at the ends of the lens fibers cannot be considered an early microscopic change.

INFLUENCE OF PRETREATMENT WITH CHEMICALS OTHER THAN CYSTEINE ON EFFECT OF LOCAL IRRADIATION OF THE RABBIT EYE WITH 1,500 R

In recent years there has been accumulated a considerable body of data bearing on the problem of increasing the radiosensitivity of living systems by chemical agents. Experimental studies on animals have been concerned with—SH-containing compounds, vitamins, antibiotics, hormones, and a metabolic poison; a much wider array of substances has been examined for their influence on the x-ray effects on bacterial growth. In the present group of experiments, eight substances in addition to cysteine, have been given a trial in the treatment of rabbits preceding the topical irradiation of their eyes.

Materials and Methods.—As in the two preceding parts of this study, a single dose of 1,500 r was applied separately to each eye of the experimental animal. The compound under investigation was either introduced intravenously prior to the irradiation of one eye or was applied locally according to a method consistent with the chemistry and toxicity of the substance.

Four sulfhydryl-containing compounds were used: glutathione, thiourea, thioglycollate, and dimercaprol (BAL). Dihydroxyacetone was employed as a reducing agent without —SH groups. *dl*-Alpha-tocopherol (phosphoric-acid disodium salt) was tested because of its antioxidant properties. Additional experiments were concerned with the citrovorum factor, a vitamin which reverses the action of folic-acid antagonists, and with a metabolic poison, potassium cyanide. The dose and form of application varied from substance to substance, so that a comparison of the potential usefulness of the individual chemicals could not be made on the basis of

the milligrams per unit of weight of the introduced material, or on the basis of the common denominator of an equal molar concentration in the aqueous humor. Whenever it was technically possible, attempts were made to determine the concentration of the medication substance in the blood and aqueous humor at various intervals after systemic administration, or in the aqueous humor alone if the compound had been introduced locally. These determinations were carried out by Dr. G. Ehrlich. In many instances she used spectrophotometric micromethods, which had been devised and elaborated by Dr. Z. Dische, of this department.[19] Dr. Dische acted also as consultant in the selection of the test substances and gave advice in many phases of the study. In the present report the emphasis has been placed on the ophthalmologic side of the investigation; the special chemical techniques which were employed and the predominantly chemical aspects of the study will be reported in another paper. The rayed animals which had been treated with the various compounds were examined routinely according to the procedures followed in the earlier parts of the investigation. The various methods of introducing the chemicals will be described briefly in connection with the results achieved with each agent or group of agents.

Results.—Experiments with Sulfhydryl-Containing Agents (Table 4): Glutathione: Four rabbits received intravenously 1 gm. of glutathione in 15 cc. of water

TABLE 4.—*Chemical Agents Other Than Cysteine Used in the Study on Protection Against X-Ray Damage to the Lens of Rabbits*

Sulfur-containing compounds	No. of Rabbits	Degree of Protection *
Glutathione		
1 gm. (intravenous)	4	0
2 gm. (intravenous)	3	++
Thiourea (intravenous)	11	+++
Thioglycollate (intravenous)	9	0
Dimercaprol (BAL) (corneal bath)	4	0
Sulfur-free compounds		
Dihydroxyacetone (intravenous)	10	0
dl-alpha tocopherol (corneal bath)	2	0
Citrovorum factor (intravenous)	9	0
Potassium cyanide (iontophoresis)	4	0

* Number of plus signs indicates the degree of protection.

one hour before irradiation of the left eyes. The right eyes had been rayed before administration of the drug. In three additional experiments the dose was increased to 2 gm. per animal. Because of the high price of the drug, the distribution of the compound in the blood and in the aqueous humor was measured only for the dose of 1 gm.

The level of the reduced form in whole blood was determined as 19 mg. per 100 cc. 30 minutes after injection; a half-hour later it had decreased to one-fifth this value. The —SH concentration in the aqueous humor measured 18 mg. per 100 cc. one hour after the intravenous introduction of the compound; at the 30-minute period the concentration had been about one-half this amount.

The rabbits which had been treated with 1 gm. of the substance and were followed for eight months showed no benefit from the treatment so far as the x-ray-induced epilation effect was concerned. Equatorial lens opacities became visible in the two eyes simultaneously from four to eight weeks after irradiation, and progressed to bilateral complete cataract between five and six months later in two animals. The three rabbits which had been given 2 gm. of glutathione were observed

19. Dische, Z., and Zil, H.: Studies on the Oxidation of Cysteine to Cystine in Lens Proteins During Cataract Formation, Am. J. Ophth. **34**:104, 1951.

for six months only. There was the same degree of epilation of the lids in the two eyes except in one animal, which showed less epilation on the protected side. In two rabbits the appearance of initial lenticular opacities was delayed from one to three weeks in the eyes which had been rayed after the injection of glutathione. One of these animals showed a total cataract in the unprotected eye 4½ months after irradiation. The third rabbit exhibited opacities of similar density in both eyes.

In these experiments, then, 1 gm. of glutathione injected one hour before the exposure to 1,500 r did not change the course of the clinically visible sign of radiation damage to the eye. Doubling this dose decreased to a moderate degree the radiosensitivity of the lens in two of three animals.

Thiourea: Thiourea was administered intravenously in a dose of 2 gm. dissolved in 15 cc. of water shortly after the right eye had been rayed and five minutes before the left eye was rayed. The concentration of the reduced form of this thiol in the blood was 100 mg. per 100 cc. 15 minutes after injection and remained high for one hour. In the aqueous humor 30 mg. per 100 cc. was measured 5 minutes after the medication and did not increase in the following 25 minutes.

Of the 13 irradiated rabbits in the series, 2 had to be discarded before radiation damage to the lens had become visible. Observations on the 11 remaining animals were maintained over a period of about six months. They conveyed the definite impression that pretreatment with thiourea exerted in a moderate but unequivocal way a protective influence against x-ray cataract. So far, total cataract has developed in the control eyes of two animals. The appearance of the initial lenticular changes was delayed from two to four weeks in the treated eyes. The cataractous lesions were in all instances more marked in the eyes which were rayed before the animals had been medicated. The difference in epilation between the right and the left eyes was not as great as it was in the cysteine experiments.

Sodium thioglycollate: On the basis of toxicity experiments, the intravenously applied dose of sodium thioglycollate had to be reduced to 0.25 and 0.5 gm. per animal. Six rabbits received the higher dose, three the lower. In connection with the lower dose, a drug level of 5 mg. per 100 cc. was determined one hour after medication in repeated experiments. At the 30-minute interval the concentration in the aqueous humor was half this amount. The injection of 0.5 gm. provided levels in the aqueous humor of 16 and 24 mg. per 100 cc. at intervals of 15 and 30 minutes, respectively, after introduction of the solution.

The development of the signs of radiation damage were followed over a period of six months in nine rabbits. In every instance epilation and cataractous changes were the same in the right and in the left eye at any time of the observation period and did not differ from the development of such changes in unmedicated, control groups. Full opacification of the lens was observed in three instances in both groups.

Dimercaprol: This drug, with its two — SH groups, has been found extremely effective in the protection of Escherichia coli [3b] against the lethal action of x-radiation. The toxicity of the substance ruled out its systemic use in rabbits, and subconjunctival injections caused severe local damage. A corneal bath with a 6% solution of the substance in peanut oil was therefore applied for five minutes to the right eye of four animals before irradiation. The rayed left eyes served as controls. The cornea of the treated eyes showed partial opacifications, which led to some scarring. Chemical determinations were carried out in two experiments only.

Thirty minutes after the corneal bath 14.7 mg. of dimercaprol per 100 cc. was measured in the aqueous humor.

Initial cataractous changes became visible in the treated and in the control eyes simultaneously about eight weeks after irradiation. No deterrent effect on x-ray damage to the eye which could be related to the action of the chemical agent was recorded.

Experiments with Chemical Agents Which Do Not Contain Sulfhydryl Groups: Dihydroxyacetone: This substance was selected among other tested reducing agents because of its relatively low toxicity for rabbits when injected into the blood stream. Two grams dissolved in 15 cc. of water was administered to 10 rabbits 15 minutes prior to irradiation of the left eye. As usual, the right eye had already been rayed.

The concentration of the chemical in the blood decreased from a value of 70 to 80 mg. per 100 cc. five minutes after injection to a value of 6 to 8 mg. per 100 cc. at the two-hour interval. The appearance curve in the aqueous humor showed a steep ascending climb, with the peak of 30 mg. per 100 cc. reached five minutes after medication. The decline of the curve was very slow for the next 15 minutes and was rapid thereafter.

In none of the treated animals was there any apparent effect on the onset and intensity of epilation. Equatorial opacities in the lens showed up in both eyes of the nine animals within the first two months after irradiation. One animal died before this time. In the following 4½ months of observation there was never the slightest indication that the treatment, applied either before or after irradiation, exerted a favorable effect. In fact, in three animals the cataractous process advanced at a faster rate in the pretreated eyes, and full cataract was seen in five of the protected eyes and in two of the nonpremedicated eyes.

Tocopherol: Tocopherol was employed for its antioxidant action. Trials with systemic or subconjunctival use of the compound were discontinued because of severe toxic reactions. It was then applied in a 3.5% solution by means of five-minute corneal baths, but even this procedure, which provided in the aqueous humor a top level of not more than 2 mg. per 100 cc. for a period of 30 minutes, was followed by severe irritation of the eyes and damage to the cornea.

An observation period of two months in two rabbits only indicated that the first signs of lens damage due to radiation were not delayed by the use of tocopherol. In view of the difficulty of introducing the substance into the chamber of the rabbit eye and its irritative qualities, no further experiments with it are contemplated.

Citrovorum factor: Citrovorum factor has been reported to shield cells against folic-acid antagonists.[20] Three milligrams of the compound ("leucovorin") was injected intravenously 30 minutes before exposure of the left eyes of nine animals to the usual dose of 1,500 r. The irradiation of the right eyes preceded the medication by a few minutes. Chemical determinations of the vitamin in body fluids were not carried out.

All animals which were followed for five months showed total epilation on both sides and typical progressive radiation cataracts of simultaneous onset and the same relatively rapid rate of spreading. Combinations of the treatment with other vitamins and other chemical agents have not yet been studied.

20. Schoenbach, E. B.; Greenspan, E. M., and Colsky, J.: Reversal of Aminopterin and Amethopterin Toxicity by Citrovorum Factor, J. A. M. A. **144**:1558, 1950.

Potassium cyanide: Experiments with potassium cyanide were undertaken because of the favorable results obtained with systemic use of the substance in mice exposed to x-radiation.[4j] A neutralized 0.5% solution of potassium cyanide was administered to four rabbits by applying the electric field at 2 ma. for five minutes with the anode on the right eye. Irradiation with 1,500 r followed after 30 minutes. The left eyes were rayed but not treated.

A relatively high concentration of cyanide can be obtained in the aqueous humor of rabbits when a solution of the salt adjusted to a pH of 7 is applied iontophoretically at 2 ma. for five minutes. In previous studies [21] determinations 30 minutes after treatment showed a concentration of 4.2 mg. per 100 cc., which decreased to one-tenth this amount in the following hour and a half. Since the quantities of cyanide in the anterior chamber did not signify whether or not adequate concentrations of the compound had entered the posterior chamber, it was thought that the results of the indophenol-oxidase reaction on the ciliary epithelium could provide evidence of the presence of the metabolic poison around the equator of the lens. There was complete, or almost complete, inhibition in the development of the color reaction in the ciliary epithelium of eyes of albino rabbits which had been treated between 30 minutes and 1 hour before the test was made.

Local cyanide treatment was not expected to affect x-ray epilation and did not do so. Moreover, in every premedicated eye typical signs of x-ray damage to the lens developed at the same time and to the same extent as in the control eyes.

Comment.—Relative protection of rats and mice against lethal doses of x-rays with various chemical agents has been reported in recent years by several groups of investigators. In addition to the outstanding results obtained with cysteine,[4f-i] benefit was also found to derive from two of the sulfur-containing compounds, glutathione [4d] and thiourea.[5] Dimercaprol, methionine, and mercaptosuccinic acid [3b] have been reported as reducing greatly the degree of damage produced in bacteria by ionizing radiation. The observations of the present study on the influence of cysteine, glutathione, and thiourea on the damaging effect of x-rays to the crystalline lens of rabbits paralleled to a certain degree the results reported on survival rates of rats and mice after total body irradiation. It was not possible, however, to evaluate the effectiveness of the intravenously used thiols on an equimolar basis of the drug levels obtained in the aqueous humor. Dimercaprol could be applied only by means of corneal baths, and it remained unclear how much of the substance actually reached the equatorial area of the lens.

Other reducing agents or antioxidants were either too toxic for such experiments ("redoxon" and tocopherol) or could not be expected to enter the intraocular fluids in sufficient concentration (ascorbic acid). The oxidoreduction potential of dihydroxyacetone is much lower than that of cysteine, and this could explain its lack of protective action.

Hormones,[22] vitamins,[4b] and antibiotics [4m] have been administered to small laboratory animals before irradiation for the purpose of studying the potential

21. von Sallmann, L.: Controversial Points in Penicillin Therapy of Ocular Diseases, Arch. Ophth. **39**:752, 1948.

22. Treadwell, Gardner, and Lawrence.[4a] Blount and Smith.[4e] Graham, J. B., and Graham, R. M.: Pharmacological Modifications of Resistance to Radiation: A Preliminary Report, Proc. Nat. Acad. Sc. **35**:102, 1949.

benefits of such pretreatment. The reported favorable results do not seem always to be of statistical significance. In the present study the influence of the citrovorum factor was tested. The effect of folic-acid antagonists ("aminopterin," amethopterin) on cells is similar to the effect of x-radiation. It was shown by Jacobson [23] that these substances arrest cell division in metaphase and induce the formation of giant epithelial cells. Citrovorum factor causes a reversal of this action of folic-acid antagonists by exerting a protective influence on the mitotic cycle. Pretreatment of rabbits with this agent did not change the course of events which follows the irradiation of the eye with 1,500 r.

The iontophoretic introduction of CN anions into the anterior segment of the eye was also completely without benefit, no protective action whatever being exhibited by the chemical. These findings are in contrast to those of Bacq and co-workers,[4j, k] who reported definite beneficial results from such treatment in mice which received total body irradiation with a lethal dose of x-rays.

SUMMARY

1. Intravenously administered cysteine had a strong protective action against radiation damage to the lens and hair follicles of rabbits when the treatment preceded the exposure of the eye to 1,500 r. This protective influence has persisted to the time of this report, at least 18 months.

2. When cysteine was injected subconjunctivally twice weekly for three weeks after the irradiation of cysteine-pretreated rabbits, the fine cortical opacities were not reduced by the additional therapy.

3. Subconjunctival injection of 1.0 cc. of an 8% solution of cysteine prior to irradiation was moderately beneficial in preventing the damage to the lens induced by local exposure of the eye to 1,500 r.

4. Analysis of microscopically visible changes in the lens, which develop in the first two or three weeks after x-irradiation with 1,500 r, showed that almost all lesions were less pronounced in the cysteine-pretreated eyes than in the eyes rayed before the use of cysteine.

5. X-ray-induced inhibition of cell division, recovery, and compensatory increase of mitotic activity of the lens epithelium differed very little in cysteine-pretreated animals and in nonpremedicated controls.

6. Under the conditions of the experiment, glutathione and thiourea were less effective than cysteine in increasing the radioresistance of sensitive elements of the lens. Sodium thioglycollate and dimercaprol (BAL) were totally ineffective. Pretreatment with other reducing chemical agents (dihydroxyacetone and tocopherol), with the citrovorum factor, and with cyanide did not reduce the injurious effect of 1,500 r applied locally to the rabbit eye.

Dr. T. H. Jukes, of the Lederle Laboratories Division of the American Cyanamid Company, provided samples of the "leucovorin" which were used in these experiments. Dr. Z. Dische and Dr. G. Ehrlich helped in the chemical part of the study, and Miss Barr assisted in determining the mitotic index of the lens epithelium.

23. Jacobson, W.: The Action of Folic Acid Antagonists on Cells, read before the Seventh International Congress of the International Society for Cell Biology, Yale University, New Haven, Conn., Sept. 4-8, 1950.

LEPTOSPIRAL UVEITIS

Report of a Bacteriologically Verified Case

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UVEITIS has been recognized as a sequel of leptospiral infection since the time of Weil.[1] In one of the four cases reported in his original publication iridocyclitis was manifested six weeks after clinical onset of the disease. Goebel,[2] in 1917, again drew attention to iridocyclitis in Leptospira icterohaemorrhagiae infections.

Since recognition of infection in man with other leptospiral strains, ocular manifestations have been observed as sequelae of canicola fever,[3] swineherd's disease,[4] mud (swamp) fever,[5] Japanese seven-day fever (nanukayami),[3b] leptospirosis australis B,[6] and Palestine bovine leptospirosis.[7] The incidence of ocular involve-

From the Walter Reed Army Medical Center, Washington, D. C., and the Veterinary Division, Army Medical Service Graduate School, and Walter Reed General Hospital.

1. Weil, A.: Über eine eigenthümliche, mit Milztumor, Icterus und Nephritis einhergehende, acute Infectionskrankheit, Deutsches Arch. klin. Med. **39**:209, 1886.

2. Goebel: Beiträge zur Frage der sogenannten Weilschen Krankheit, Med. Klin. **12**:381, 1916.

3. (*a*) Legras, A. M., and Wolters, D. H. F.: Ophthalmologic Complications in a Case of Weil's Disease Typhus Canicola, Ophthalmologica **99**:469 (May) 1940. (*b*) Doret, M., and Rohm, A.: Augenkomplikationen bei benignen Leptospirosen, Klin. Monatsbl. Augenh. **118**:51 (Jan.) 1951.

4. (*a*) Babel, J.: Les complications oculaires des leptospiroses benignes, Bull. et mém. Soc. franç. opht. **59**:292, 1940-1946. (*b*) Gsell, O.; Rehsteiner, K., and Verrey, F.: Iridocyclitis als Spätfolge von Leptospirosis Pomona, Ophthalmologica **112**:320 (Dec.) 1946. (*c*) Beeson, P. B.; Hankey, D. D., and Cooper, C. F., Jr.: Leptospiral Iridocyclitis, J. A. M. A. **145**:229 (Jan. 27) 1951.

5. Glaser, W.: Das Schlamm- oder Erntefieber im Bezirksamt Erding im Jahre 1927, München. med. Wchnschr. **75**:1162, 1928. Reimer, L.: Die Leptospiren-Uveitis, Klin. Monatsbl. Augenh. **118**:476 (May) 1951.

6. Johnson, D. W.: The Australian Leptospiroses, M. J. Australia **2**:724 (Nov. 11) 1950.

7. Feigenbaum, A., and Landau, J.: Uveitis Due to Bovine Leptospiroses, Acta med. orient. **7**:115, 1948.

ment in the leptospiroses has been varyingly reported as from 10 to 44%.[8] This variation reflects the intensity of the search for ocular manifestations. Although not reported in the literature available to us, uveitis is undoubtedly associated with the other leptospiroses of man.

Ocular involvement in the leptospiroses may appear as early as the second week of illness [8a] or as late as one year after systemic manifestations.[8b] In the majority of cases reported, iritis, iridocyclitis, and chorioretinitis appeared between the first and the sixth month after systemic infection. Because of this delayed appearance, Walch-Sorgdrager [8c] posed the question, "Should the leptospirae themselves or their toxins be held responsible for the appearance of iritis?" As far as we can determine, no prior isolation of leptospirae from the eye in human beings has been reported.

A case of uveitis in which leptospiral invasion of the aqueous humor was bacteriologically proved is presented.

REPORT OF CASE

Systemic Phase.—On July 12, 1951, one of us (A. A.) accidentally contaminated his left eye while working with a culture of Leptospira alexi.[9] He immediately rinsed the eye with a boric acid solution and the face and scalp with 70% alcohol. There were no symptoms until July 23, when he had sudden onset of severe frontal headache, generalized aches and pains, and profound weakness. The temperature was 104.5 F. The patient was given 600,000 units of aqueous penicillin procaine. The temperature remained elevated throughout the night, and his symptoms were essentially unchanged the following day. He was hospitalized on July 24; and on admission the temperature was 102 F., the pulse rate 96 per minute, the respiration rate 20 per minute, and the blood pressure 120/70. Examination revealed that the patient was acutely ill but well oriented. The skin was dry and flushed, but there was no evidence of jaundice. Physical examination revealed an essentially normal condition except for distinct redness of the margins of the eyelids. Injection of the conjunctival vessels was not marked. Some resistance was felt two to three fingerbreadths below the right costal margin, but the liver edge could not be palpated. The spleen likewise could not be felt. Neurological examination revealed no abnormality.

The day after admission the temperature dropped to 98.8 F., but during the following four days it steadily rose, until on July 28 it reached a peak of 107 F. On July 26, the liver edge became palpable three fingerbreadths below the costal margin. However, even at the height of the fever no other physical signs could be elicited, and the patient at no time showed evidence of disturbed sensorium or meningeal irritation. On July 28, 500 mg. of chloramphenicol was administered by mouth every six hours and the treatment continued through Aug. 6. When the temperature reached its greatest height (107 F.), the patient was given cold water retention enemas, salicylates, and intravenous injections of dextrose and saline solution. The following day the temperature was 102.2 F., and it continued to fall until it reached normal on Aug. 1, where it remained except for a sudden rise to 101 F. on Aug. 6. From July 29 until Aug. 2 the illness was characterized by marked prostration, anorexia, and profuse sweating. During this period the patient was given three daily intramuscular injections of 5 cc. of desoxycorticosterone acetate. Convalescence was uneventful, and the patient recovered strength and appetite. The liver became smaller but was still palpable 1 fingerbreadth below the costal margin on the day of discharge from the hospital, on Aug. 9, and remained enlarged for approximately two weeks thereafter.

The temperature curve and significant laboratory findings are shown in the accompanying chart.

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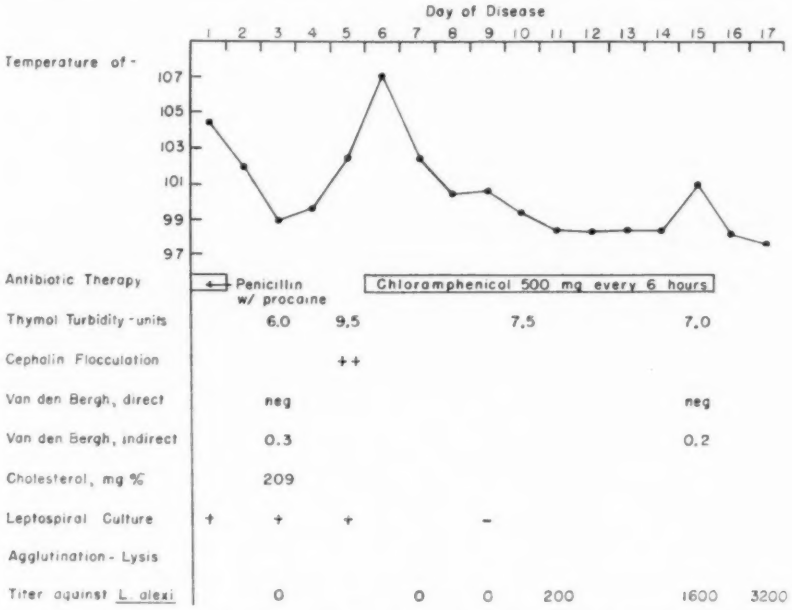
8. (*a*) Strassburger, J.: Zur Klinik der Weilschen Krankheit, Deutsches Arch. klin. Med. **125**:108, 1918. (*b*) Patterson, H. M.: Weil's Disease: Observation in 61 Cases, J. A. M. A. **134**:1077 (July 26) 1947. (*c*) Walch-Sorgdrager, B.: Leptospiroses, Bull. Health Organ., League of Nations **8**:144, 1939.

9. Unpublished data from the laboratories of the Army Medical Service Graduate School.

The serum albumin, globulin, and total protein were within normal limits. The urine was normal. The sedimentation rate on the third day of illness was 34 mm. (Wintrobe), and the hematocrit reading was 49.

The leucocyte count on July 28, before the peak of the fever, was 7,150 per cubic millimeter (segmented polymorphonuclear leucocytes, 63%; band forms, 5%; lymphocytes, 32%). Later the same day, at the height of the fever, the white cell count was 11,350 (segmented polymorphonuclear leucocytes, 78%; band forms, 1%; lymphocytes, 21%). A spinal puncture performed within the same hour revealed clear fluid under a pressure of 240 mm. of water, with 2 white cells per cubic millimeter. Routine culture yielded no pathogens. The protein measured 54 mg.; the chlorides, 693 mg., and the sugar, 88 mg., per 100 cc. The colloidal gold curve was zero (normal) throughout; the Kolmer reaction was negative. Unfortunately, the spinal fluid was not cultured for leptospirae.



Temperature curve and laboratory findings in a case of leptospiral uveitis treated with antibiotics.

Latent Uveitis.—While at work during the day of Sept. 11, 51 days after onset of the systemic illness, the patient noticed blurring of vision in the left eye. This was slight, and there was no redness or pain in the eye. On the following day he was examined in the eye clinic, and a diagnosis of uveitis in the left eye was made. The patient was hospitalized for further study and treatment. The past history was essentially noncontributory except for the leptospirosis, as previously shown.

The general physical condition was normal. Ophthalmologic examination revealed that vision without glasses was 20/30 in the right eye, correctible to 20/15, and 20/25, in the left eye, correctible to 20/15—2. The external appearance of the right eye was normal. Slit-lamp examination of the left eye showed a collection of medium-sized keratic precipitates located centrally. There was a generalized meshwork of finer deposits over the entire endothelium. A + 1 aqueous beam and a few cells could be seen in the anterior chamber. The iris was normal. There was no formation of synechiae. The lens, media, and fundi were normal.

Routine complete laboratory examinations, including a serologic test for syphilis, gave normal results. A survey revealed no foci of infection. Skin tests for tuberculosis and brucellosis gave negative reactions. Examinations of the ear, nose, and throat revealed a normal condition except for bilateral clouding of the antrum, reported on x-ray examination of the sinuses. This was thought to be due to a mild infection of the upper respiratory tract, present at the time of examination. Genitourinary examination revealed a somewhat enlarged, firm prostate. Microscopically, the prostatic secretion was normal. An intravenous pyelogram showed prompt excretion bilaterally, with no gross abnormality of the urinary tract. A culture of the prostatic secretion was negative for leptospirae. The medical consultant found no evidence of any generalized medical disease, and the electrocardiogram was normal. Because of the complaint of low-back pain, roentgenograms of the lumbosacral portion of the spine were made but failed to reveal any bony abnormality. A leptospiral agglutination test was positive in a dilution of 1 : 3,200.

Course in Hospital: On the day following admission a puncture of the anterior chamber of the left eye was performed, and leptospiral culture media were inoculated with the material obtained. Examination of the cultures on the 18th day of incubation revealed the presence of leptospirae, later identified as Lept. alexi, the same strain as that isolated from the blood during the previous illness. On the evening of the day on which the anterior-chamber puncture was performed, 20,000,000 organisms of monovalent typhoid vaccine was given intravenously. The temperature rose to 101.6 F. on the following day and subsided to normal the next day. At this time 40,000,000 typhoid organisms were administered intravenously but failed to incite any febrile response. Streptomycin, in a dose of 0.5 gm., was given by intramuscular injection twice a day, beginning the day after admission, and was continued for two weeks. Local treatment during this time consisted of atropinization of the eye, light protection, and subconjunctival injection of epinephrine solution. Slit-lamp examination revealed an increase in the keratic deposits on the posterior surface of the cornea, a +1 aqueous flare, many cells, and numerous aggregates of cells on the entire pupillary margin of the iris. The vitreous remained clear except for a few pigmented clumps of cells anteriorly. Small deposits were seen on the posterior surface of the lens.

At this time artificial fever therapy was started by means of the Hypertherm (cabinet). After the first treatment, the intensity of the aqueous flare diminished; there were fewer cells, and the deposits on the pupillary margin of the iris disappeared. Fever treatments were given every other day for a total of six treatments. After the fourth treatment the meshwork of keratic precipitates was seen to have disappeared, leaving only the isolated, smaller deposits, which were darker. An occasional cell was noted, and a questionable flare remained. At this time streptomycin was discontinued, and 250 mg. of chloramphenicol was given by mouth, four times a day. After the fifth fever treatment only an occasional cell and a questionable aqueous flare were present. After the sixth fever treatment (Oct. 11), the patient was discharged from the hospital, and there was no sign of active inflammation in the left eye. The only evidence of the past inflammation was the presence of an occasional small keratic precipitate on the cornea.

There has been no recurrence of the inflammation.

COMMENT

Mode of Infection.—The eye as a portal of entry for leptospiral infections has been reported by van Thiel.[10] In this case the time and manner of leptospiral infection, as well as the strain involved, were definitely known. The incubation period preceding clinical onset of illness was 12 days.

Therapy in the Systemic Phase.—Despite the reported therapeutic efficacy of the several antibiotics in the treatment of human leptospirosis, experience in this case supports the findings of Hall [11] and his associates. In their studies, penicillin, streptomycin, aureomycin, terramycin, and chloramphenicol were evaluated as thera-

10. van Thiel, P. H.: The Leptospiroses, Leiden, Universitaire Pers Leiden, 1948.

11. Hall, H. E.; Hightower, J. A.; Rivera, R. D.; Byrne, R. J.; Smadel, J. E., and Woodward, T. E.: Evaluation of Antibiotic Therapy in Human Leptospirosis, Ann. Int. Med. **35**:981 (Nov.) 1951.

peutic agents in 67 cases of leptospirosis in Puerto Rico. They found that the antibiotics employed demonstrated no appreciable effect upon the clinical course of leptospirosis in man, even when the drugs were administered relatively early in the course of the disease. There was no apparent beneficial influence on the febrile course, on prevention or shortening of the period of jaundice, on reduction of symptoms referable to the central nervous system, or on lessening of the degree of renal involvement. The duration of leptospiremia and the persistence of the organism in the cerebrospinal fluid were not appreciably altered by any of the antibiotics employed. In the words of these authors, "It is doubtful whether any of the antibiotics employed are worthy of future use in the treatment of patients with leptospirosis."

Latent Uveitis.—The aqueous humor as a nesting site for leptospirae assumes significance when consideration is given to the transitory nature of leptospiral invasion of the blood stream and cerebrospinal fluid. The coexistence of living virulent organisms in the aqueous humor and the extremely high blood levels of specific agglutinating antibodies may possibly be explained by the paucity of proteinaceous material in the aqueous humor. Aqueous humoral levels for agglutinins of other bacterial agents are reportedly [12] as low as 1/2,000th of the blood concentration. In leptospiral uveitis aqueous humoral agglutination-lysis titers ranging from 0 to 1:20 have been reported,[13] while serum titers were in the order of 1:800 to 1:16,000. However, after puncture of the anterior chamber, the re-formed aqueous has been shown [12] to contain antibodies in considerably augmented quantity. This increase in antibody content is probably the reason that anterior-chamber puncture is of therapeutic value in cases of bacterial uveitis.

In the case reported, isolation of leptospirae from the aqueous was made early in the course of uveitis, presumably before local tissue-antibody reaction could be manifested. At this time the patient's serum-agglutinating-antibody titer was 1:3,200, the peak titer of 1:6,400 having been attained one week prior to onset of the uveitis.

Clinical Diagnosis.—The ocular manifestations of the leptospiroses do not present a distinct clinical entity. Similar pathologic findings may be encountered in syphilis, brucellosis, tuberculosis, and nonspecific uveitis. Clinical diagnosis of leptospiral uveitis necessarily rests upon information elicited from the history of the patient. A history of febrile, influenza-like disease, a bout of jaundice, or bacteriologically undiagnosed meningitis occurring two weeks to one year prior to onset of uveitis is particularly significant. However, in many instances the systemic phase of the leptospiroses may be subclinical, or of such low order as to be overlooked. In all cases, therefore, consideration should be given to the patient's occupation and environment as potential sources of leptospiral infection.[14] Dairymen, swineherds, kennelmen, abattoir workers, fish and poultry packers, and sewer workers are exposed to occupational hazard. Rat infestation of the home, associated with sick dogs, or swimming in suspect waters may be of significance. In all instances, laboratory confirmation of the clinical diagnosis is essential.

12. Woods, A. C.: Allergy and Immunity in Ophthalmology, Baltimore, Johns Hopkins Press, 1933.

13. Gsell, Rehsteiner, and Verrey.[4b] Doret and Rohm.[3b]

14. Hanno, H. A., and Cleveland, A. F.: Leptospiral Uveitis, Am. J. Ophth. **32**:1564 (Nov.) 1949.

Laboratory Diagnosis.—Leptospiral uveitis is oftenest first manifested after the systemic infection has run its course. Serum-antibody levels have passed their peak titer. The dramatic rise in titer of diagnostic significance in the systemic phase is no longer demonstrable. However, as the population of the United States at large has had little experience with the leptospiroses, serum-agglutinating-antibody titers in excess of 1:400, even though obtained from but a single specimen, must be considered significant in cases of uveitis. The experience of Beeson and associates [4c] demonstrates the value of routine serologic examination for leptospirosis in the diagnosis of uveitis. Serologic examination may be made by the agglutination-lysis test of Schuffner and Mochtar [15] or by the agglutination test employing formalized antigens, as recommended by Ward.[16] In addition, puncture of the anterior chamber and culture of the aqueous on appropriate leptospiral media not only may afford bacteriological proof of leptospirosis, but also may permit subsequent definitive identification of the infecting strain.

Treatment of the Uveitis.—In leptospiral uveitis, as in the other types of uveitis, the usual therapeutic measures, such as immediate and continued dilation of the pupil and light protection, are of primary importance.

It is our impression that neither antibiotic employed influenced the clinical response of the patient. Failure of intravenous administration of typhoid vaccine to incite an adequate febrile response precludes evaluation of this therapeutic measure. We believe that the course of the uveitis was favorably influenced by means of artificial fever induced by the Hypertherm (cabinet).

Paracentesis of the anterior chamber is a recognized procedure which, in our opinion, should be employed oftener, for both diagnostic and therapeutic reasons.

SUMMARY

A case of bacteriologically proved leptospiral uveitis is reported. Uveitis first appeared 51 days after clinical onset of systemic illness.

Infection resulted from a laboratory accident in which leptospirae were splashed upon the face and left eye. The incubation period was 12 days.

Laboratory diagnosis was first confirmed by blood culture, prior to the patient's antibody response.

Chloramphenicol therapy in the systemic phase and streptomycin and chloramphenicol therapy in the uveitic phase were without influence on the clinical response.

Coexistence of living pathogenic leptospirae nesting in the aqueous fluid and of high serum-antibody levels was established.

The diagnostic value of direct leptospiral culture of body fluids is demonstrated.

The commonly employed measures of dilation of the pupil, light protection, and artificial fever (Hypertherm [cabinet]) are indicated in the therapy of leptospiral uveitis, as well as paracentesis of the anterior chamber for both diagnosis and therapy.

15. Schuffner, W., and Mochtar, A.: Versuche zur Aufteilung von Leptospirenstammen mit einleitenden Bemerkungen über den Verlauf von Agglutination und Lysis, Zentralbl. Bakt. **101**:405 (Feb.) 1927.

16. Ward, M. K.: Personal communication to the authors.

OCULAR AND SUBCUTANEOUS INFLAMMATORY RESPONSES TO TRANSPLANTATION OF HETEROLOGOUS TUMORS

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THIS INVESTIGATION was undertaken to study the differences between the ocular and the subcutaneous inflammatory responses following heterologous tumor transplantation, and to determine whether such differences could account for the superiority of the ocular route as a transplantation site.

That such differences do occur appears to have been taken as self-evident in many of the published reports dealing with the ocular transplantation of tumors. For example, Smirnova [1] assumed that the "agents of defense" could not act in the anterior chamber but presented no evidence to support this hypothesis. Greene [2] stated that the eye differs from other transplantation sites in the rapidity and intensity of foreign-body reactions. Greene, furthermore, concluded that these differences account for the success of transplants in the ocular area. On the other hand, Morris and associates [3] described destruction of tumor heterotransplants in the eye by lymphocytes, plasma cells, and, occasionally, foreign body giant cells. These authors did not indicate how the rate and intensity of the ocular reactions compared with the reactions following transplantation in other areas. Massina [4] reported successful ocular heterotransplantation in the presence of intense inflammatory reactions.

In general, it is apparent, usually by inference, that most observers find that the inflammatory reactions to tumor heterotransplants in the eye are weaker than those to transplants in other areas. In order to provide specific evidence on this point, my colleagues and I have observed the early course of the responses to intraocular and to subcutaneous tumor heterotransplants, comparing the reactions in these two areas in rate, intensity, and character.

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1. Smirnova, E.: La greffe hétérogène des tumeurs malignes, Bull. biol. et med. exper. U. S. S. R. **4**:6-10, 1937.

2. Greene, H. S. N.: Heterologous Transplantation of Mouse Tumors Induced in Vitro, Cancer Res. **6**:396-402, 1946.

3. Morris, D. S.; McDonald, J. R., and Mann, F. C.: Intraocular Transplantation of Heterologous Tissues, Cancer Res. **10**:36-48, 1950.

4. Massina, M. H.: Biological Assay of Human Kidney Tumors by Means of Heterologous Ocular Transplantations: A Study of Clear-Cell Carcinoma, Granular-Cell Carcinoma and Papilliferous Epithelioma of the Kidney, J. Urol. **58**:1-9, 1947.

METHODS AND MATERIAL

Our methods of anterior-chamber and of subcutaneous transplantations have been described.[5] In each case the material to be transplanted was introduced by means of trocars of constant bore, through prepared incisions in the skin or cornea. The subcutaneous transplants were deposited several centimeters from the cutaneous incision, so that the trauma in the immediate neighborhood of the transplant consisted only of the spreading of the tissues attendant upon the passage of the blunt trocar. The subcutaneous transplants were made easily without anesthesia after the area had been shaved and washed, whereas in the case of anterior-chamber transplants intraperitoneal injection of pentobarbital was used for general anesthesia. The dose of transplanted material was similar in the two areas. Guinea pigs were used in all experiments. The animals were maintained in each case under identical conditions, often in the same cages. For histological study the subcutaneous transplants were removed immediately after the animal was killed by approaching them from the lower, or muscular, surface. The ocular samples were obtained by removing the eyes *in toto*. All tissues for histological examination were fixed in Zenker's fluid. Sections cut from paraffin blocks were stained with hematoxylin and eosin.

The tumor which we have most extensively studied is the laboratory tumor MT8. This is a readily transplantable mouse tumor, which has grown well in the guinea pig eye. It is maintained in C3H mice by serial subcutaneous transfer about every two months. Our previous experiences with this tumor have been reported.[6] It usually evokes considerable gross inflammatory reaction in the guinea-pig eye, with haziness, edema, and vascularization of the cornea and injection of the conjunctiva. These inflammatory phenomena often decrease after five or six days and may be much diminished when maximum growth is attained, at about 14 days. The gross inflammatory reactions are not as prominent when transplants of MT8 are made from samples already growing in the guinea-pig eye. Likewise, the reactions on the part of the subcutaneous tissues are slightly less vigorous in response to transplants which have been passed through one or more generations in the guinea-pig eye. However, the general character of the reactions in both areas is modified remarkably little by prior passage in the guinea-pig eye, and separate treatment is unnecessary.

OBSERVATIONS

Inflammatory Reaction to MT8 in the Guinea-Pig Eye.—In the first four or five days of residence of the tumor in the eye (Fig. 1 *A* and *B*) considerable portions might appear to be degenerating or were actually necrotic. The portions lying nearest the iris were best preserved. The vessels of the iris in the neighborhood of the tumor were dilated, and endothelial proliferation and new capillary formation were evident. The continuity of the iris surface was destroyed, and the tumor rested partly within the stroma of the iris; invasion often had already begun; mitotic figures were present.

The inflammatory-cell response in the stroma of the iris was invariably mild. A few, and occasionally many, eosinophiles were observed. Rarely, a few polymorphonuclear leucocytes marginated on the capillary walls. Macrophages and lymphocytes were sparse or absent in the adjacent iris. However, on the aqueous surface of the tumor were frequent collections of engorged macrophages, with mitotic figures among them. Fibroblasts were not in evidence, and the connective tissue cells of the iris showed no evidence of proliferation where the tumor met them. However,

5. Snell, A. C., Jr., and Favata, B. V.: Development of Resistance to Reinoculation and of Circulating Cytotoxins in Response to Heterologous Ocular Tumor Transplantation in the Guinea-Pig, Cancer Res. **11**:335-340, 1951.

6. (*a*) Snell and Favata.[5] (*b*) Schilling, J. A.; Snell, A. C., Jr., and Favata, B. V.: Heterologous Ocular Transplantation as a Practical Test for Cancer, Cancer **2**:480-490, 1949.

traces of connective-tissue proliferation might be seen on the surface of the iris between the transplanted tumor and the angle of the anterior chamber. Small amounts of fibrin and free red blood cells might be present in the anterior chamber, usually at the angle.

At seven or eight days the pattern of the response was scarcely altered (Fig. 2*A*). When the transplant grew, the remains of the iris became telescoped against the ciliary body. The iris stroma had disappeared or was so distended by actively growing tumor as to be unrecognizable. The invading tumor was not infiltrated with inflammatory cells or fibroblasts. The aqueous surface of the transplant was usually covered with a mantle of large macrophages, and necrotic remains were not in evidence. Lymphocytes were seen in small numbers in the ciliary body. The overlying cornea was frequently edematous and vascularized and contained numerous small and large wandering cells.

Some samples of this tumor seven or eight days after transplantation in the eye showed distinctly less evidence of profuse growth (Fig. 2*B*). While apparently healthy tumor cells might be present deep in the iris, they were scattered, and intermingled with small and large macrophages. Central portions of the tumor were necrotic, and a partially encapsulating and invading fibroblastic response had occurred. Fibroblasts, when they appeared, invariably were most prominent at the peripheral, or ciliary, margin of the transplant on its anterior aspect and were found along the surface of the iris all the way to its root. It is probable that those transplants which become infiltrated with fibroblasts and macrophages belong in the group in which "takes" do not occur, which constitutes about 50% of ocular transplants of this tumor.

The regressing stages of the transplant were associated with increasing numbers of lymphocytes and delicate, mostly collagen-free, fibroblastic encapsulation, which occurred especially on the anterior surface of the tumor. This stage was marked in the gross by a rapid fading of the light-pink color characteristic of growing transplants and occurred without external evidence of increased ocular irritation.

Inflammatory Response to MT8 in the Subcutaneous Tissues of the Guinea-Pig.—At four days (Fig. 3*A*) there was a vigorous response by the subcutaneous tissues, the most prominent feature of which was the fibroblastic reaction. Layers of young fibroblasts surrounded and invaded the transplant. The capillaries were distended, and perhaps proliferating. Numerous macrophages, of various sizes, were interspersed among the fibroblasts. A few polymorphonuclear leucocytes were occasionally seen, and small numbers of eosinophiles were almost invariably present. Small numbers of extravascular red blood cells were seen commonly. Lymphocytes were sparse. The tumor was scattered and degenerating.

At eight days (Fig. 3*B*) the connective-tissue reaction was profuse and extensive. Much collagen had been laid down and encapsulating, and interlacing fibers were seen about and all through the area of the transplant. No tumor was recognizable. Many macrophages and a few lymphocytes were present.

Inflammatory Response to a Human Carcinoma Transplanted into the Eye and into the Subcutaneous Tissues of the Guinea Pig.—This mammary carcinoma and its extraordinary capacity to grow in the guinea-pig eye have been described in previous reports.[6b] Samples of the reactions produced by this tumor in the third guinea-pig passage, three days after transplantation into the eye and into the sub-

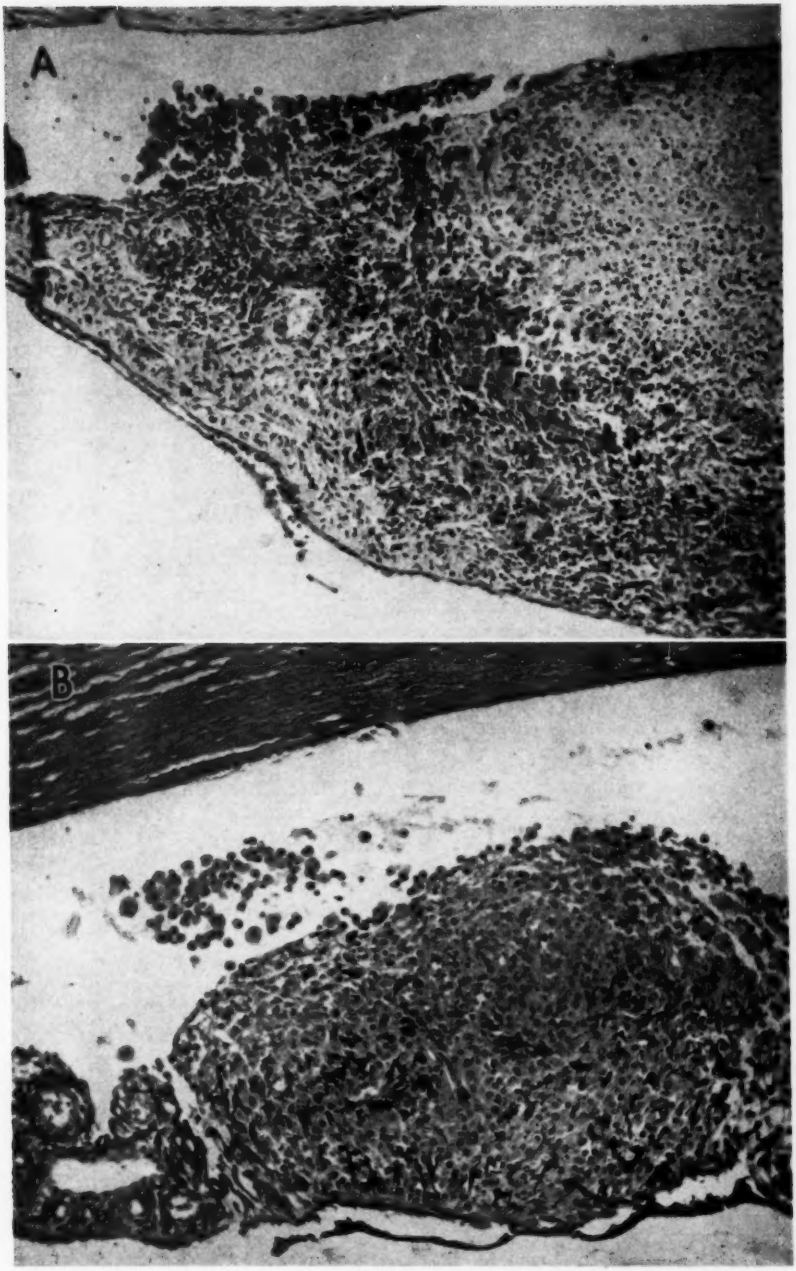

Fig. 1.—Anterior-chamber transplant of MT8 (*A*) at four days and (*B*) at five days.

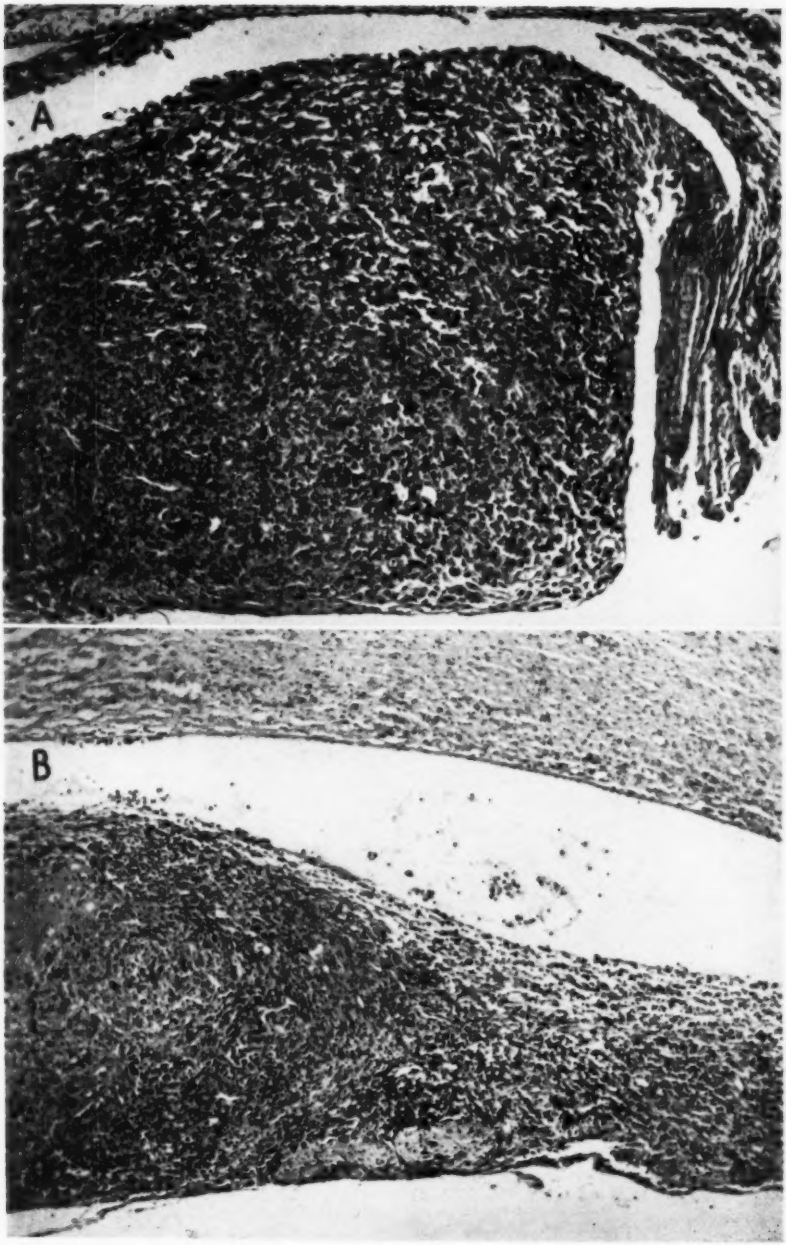

Fig. 2.—Anterior-chamber transplant of MT8 (*A*) at seven days and (*B*) at eight days, with fibroblastic reaction.

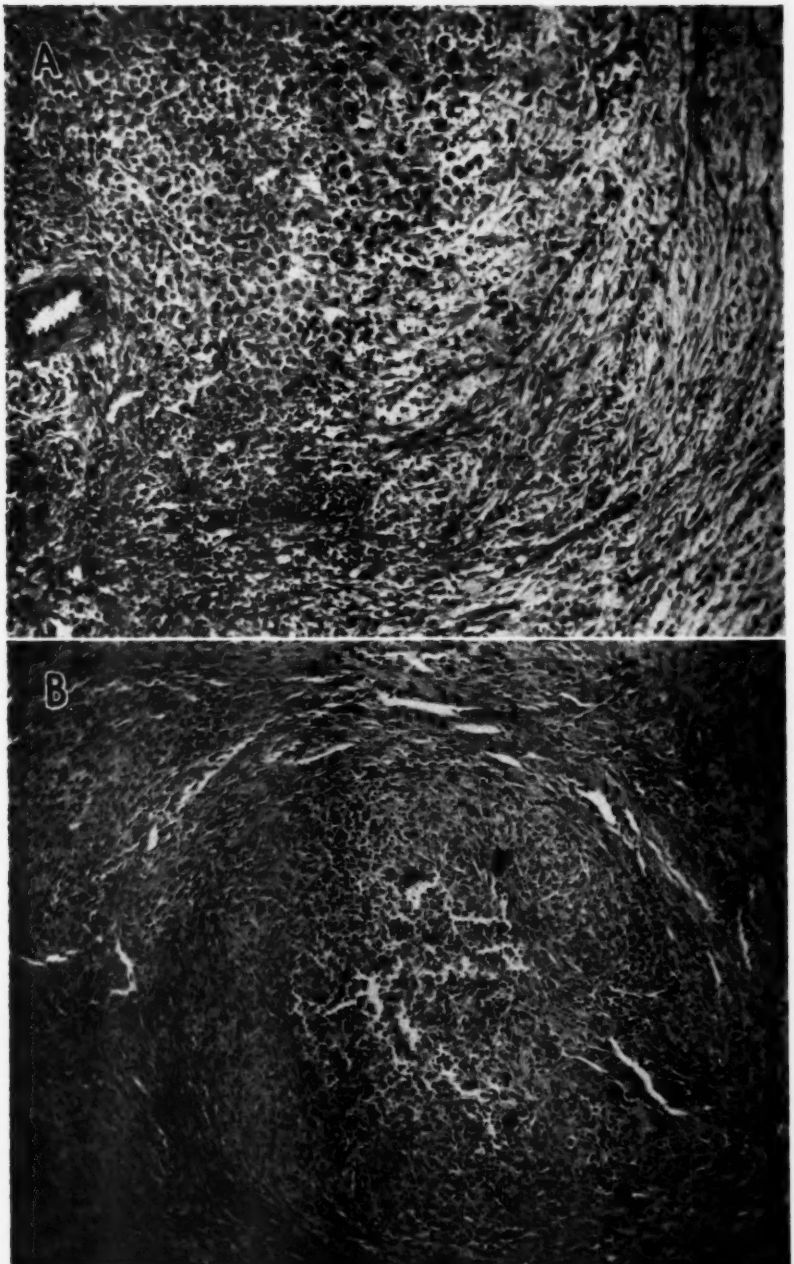

Fig. 3.—Subcutaneous transplant of MT8 (*A*) at four days and (*B*) at eight days.

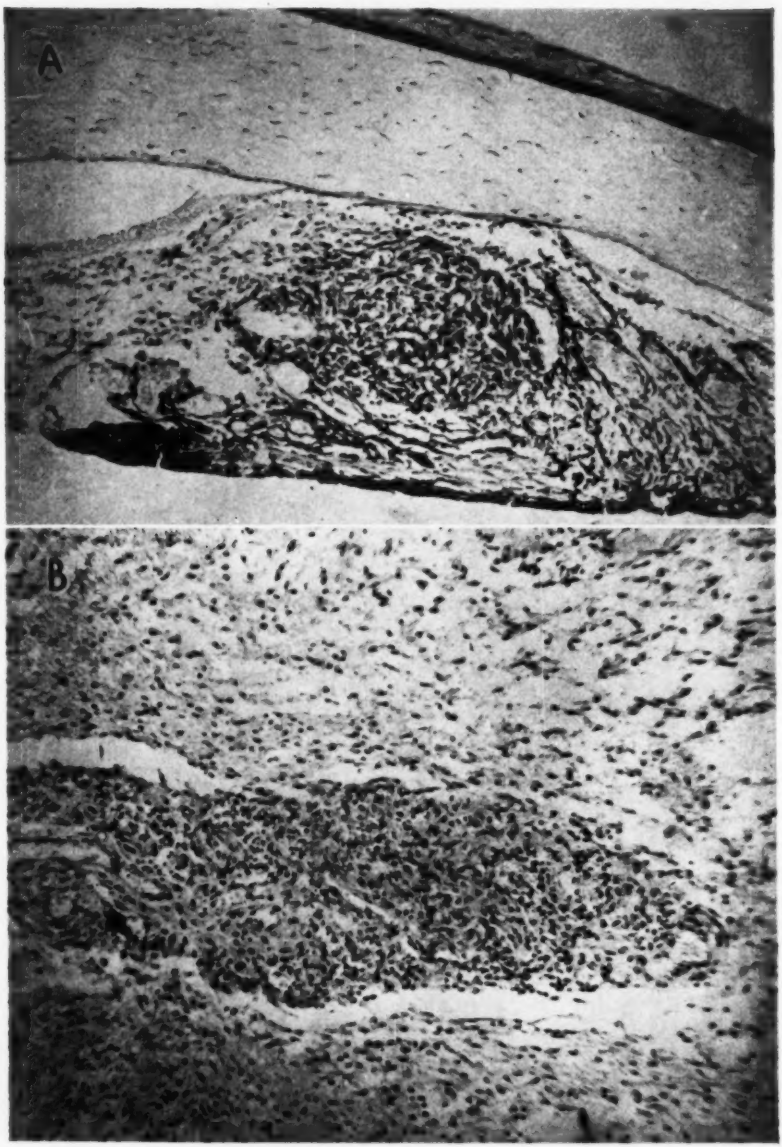

Fig. 4.—Anterior-chamber transplant of human carcinoma (*A*) at three days and (*B*) subcutaneous transplant of human carcinoma at three days.

cutaneous tissues, are included as further instances of the difference in the reactions in these two sites. In the eye (Fig. 4*A*) much of the tumor was necrotic, but a small portion retained its morphological and staining characteristics. It was closely related to engorged iris vessels. There was no inflammatory-cell infiltration of the distorted iris stroma adjacent to the tumor. Some hemorrhage was present in the anterior chamber, and there was a narrow layer of fibrin on the iris surface and overlying the tumor. Along this strip of fibrin were seen a few elongated cells resembling fibroblasts; these cells extended along the iris surface and connected with the iris at a point distant from the implant. In the subcutaneous tissues (Fig. 4*B*) the tumor was also necrotic in places, and in others, morphologically intact. There was a distinct and wide mantle of delicate fibroblasts surrounding and invading the tumor. Dilated capillaries and free blood were present, and macrophages were fairly numerous.

COMMENT

The inflammatory response on the part of the eye following transplantation of the tumors described is decidedly less vigorous in rate and in quantity than that of the subcutaneous tissues. However, study of the preparations fails to indicate with certainty whether this is a difference in kind as well as in degree. Nevertheless, one gets a strong impression that in the eye the round-cell and macrophagic response occurs with greater facility than the fibroblastic response. On the other hand, the early reaction of the subcutaneous tissues is made up of an intense fibroblastic, as well as macrophagic, response. The vascular response in the two areas is similar.

In some instances, a mild fibroblastic response on the part of the eye does occur. These fibroblasts do not appear in the iris against which the tumor lies or in the iris which is being invaded by the transplanted tumor, in spite of the presence of vascularization of the tumor at this interface. When fibroblasts appear, they approach the tumor along the anterior surface of the intact peripheral portions of the iris as though orginating at a distant point in the angle of the anterior chamber. In some cases this reaction appears to be sufficient to arrest or prevent local growth of the transplanted tissue. In no instance of the ocular transplants is the fibroblastic reaction as intense as in any instance of the subcutaneous transplants.

The differences in the inflammatory response to transplanted heterologous tumors on the part of the eye as compared with the responses of the subcutaneous tissues suggest the hypothesis that these differences account for the superiority of the eye as a site for tumor heterotransplantation. This hypothesis is attractive because it is consistent with the well-recognized weakness of fibroblastic activity on the part of the iris following surgical or accidental trauma; in fact, this consideration gives rise to the speculation that the weakness in fibroblastosis is the critical factor in the superiority of the eye as a transplantation site.

The defense of the mammalian organism against transplantation is of two kinds. The first is the foreign-body reaction, made up mostly of fibroblasts and macrophages. The second is the lymphocytic-immunological response. In the case of heterologously transplanted tissue, the first type of reaction occurs quickly and intensely, followed and overlapped by the second. In the case of homologous transplantations, however, the first type of reaction occurs feebly or not at all, and destruction of the graft is achieved by the more specific and more leisurely immunological mechanism, often after a period of temporary growth. If this scheme is

correct, then heterotransplants, made in an area where foreign-body reactions are suppressed, should behave as homotransplants. This is much the case of heterotransplants of tumor in the anterior chamber. They are found to excite relatively little foreign-body reaction, and their behavior of temporary growth, followed by ultimate regression, may be compared with that of many homologously grafted tumors in other sites.

The observations described in this report support the principle that successful intraocular tumor heterotransplantations occur in association with feeble connective-tissue and macrophagic responses. It should be clearly recognized that the association does not constitute proof of a causal relationship between the degree of inflammatory response and the success of the transplant.

SUMMARY

Transplants of the mouse carcinoma MT8 in the guinea-pig eye excite a relatively mild macrophagic and fibroblastic reaction. In contrast, the subcutaneous tissues of the guinea pig react to transplants of this tumor with a moderate macrophagic and an intense fibroblastic response. This observation supports the hypothesis that these differences account for the superiority of the eye over the subcutaneous tissues as a site for the heterotransplantation of malignant tumors.

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USE OF TYPHOID VACCINE IN CONTINUOUS INTRAVENOUS INFUSION IN TREATMENT OF EYE DISEASES

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TECHNIQUE AND MATERIALS

ADMINISTRATION of the continuous type of typhoid infusion which is presented here is usually started early in the morning on a fasting stomach. The patient is covered with one blanket to about the level of the shoulders. It is not necessary to have a nurse in constant attendance, as is the case in the methods described by Solomon and Somkin [1] and by Curry and Shaw.[2] The reason for this is that no dangerous temperature levels will be reached provided the infusion is given at the recommended rate and dilution.

Two cubic centimeters of triple typhoid vaccine, containing 1,000,000,000 killed typhoid organisms per cubic centimeter, is introduced into an infusion flask containing 1 liter of sterile isotonic saline solution. The flask is then shaken so as to make a homogeneous suspension of the dead bacteria. With the patient lying in bed, a 22-gauge intravenous needle, connected by a plastic tube to the infusion flask, is inserted into an antecubital vein and the infusion started. The rate of infusion is set at between 20 and 25 drops per minute. The patient's arm is not immobilized, and he is instructed to move his arm gently from side to side occasionally, without flexing it at the elbow. The patient is also instructed to massage the arm and forearm receiving the infusion at intervals of 10 minutes with the hand of his opposite arm. Both these procedures help to alleviate the pain and numbness that usually develop in the extremity after the fluid has been flowing in for some time. The temperature is checked orally every 30 minutes until the infusion is completed. After that the temperature is checked every two hours until it normalizes. The flask is shaken at intervals of 15 minutes to make sure that the patient receives a more or less homogeneous suspension of the bacteria in the solution. Quite often, after the infusion has been given for about 30 minutes, the patient has a chill, which can be controlled by giving 50 mg. of meperidine (demerol®) hydrochloride intramuscularly. The same amount of meperidine can be repeated at three- to four-hour intervals if necessary to ease the discomfort of headache, general malaise, gastrointestinal upset, or nervousness. No antipyretic or analgesic is administered during the treatment until the temperature has dropped to a normal level. Lunch is withheld, for obvious reasons. Many patients are, however, able to eat a light supper. The infusion is usually completed in about 7 to 10 hours.

The treatment may be repeated within 48 to 72 hours after the beginning of the first infusion if necessary. In many cases of iritis and iridocyclitis one treatment may be all that is required. The rate of infusion is the same in all the treatments. Not more than four or five courses of treatment are advised. If the patient is not benefited by four or five infusions, it is wise to try other forms of therapy.

1. Solomon, H. A., and Somkin, E.: An Improved Method of Obtaining Sustained Controlled Hyperpyrexia with Triple Typhoid Vaccine, Am. J. M. Sc. **203**:736, 1942.

2. Curry, J. J., and Shaw, E. A.: Continuous Intravenous Injection of Typhoid Vaccine in Treatment of Certain Ophthalmic Diseases, Arch. Ophth. **42**:123, 1949.

BEARING OF METHOD ON PREVIOUS METHODS

This form of administering typhoid vaccine is similar to the rapid injection only in that both are given intravenously. It differs from the latter in the following respects: Hyperpyrexia is not produced; the systemic reaction is uniform and slight; the total number of killed typhoid organisms administered in one treatment is many times as large (20 to 200 times as large), and the number of organisms administered at each treatment is the same. In the rapid form of injection a correspondingly increasing number of bacteria is given.

The method under discussion in this paper is similar to the methods advocated by Solomon and Somkin [1] and Curry and Shaw [2] in that huge doses are administered. It differs in that the production of hyperpyrexia is not the therapeutic objective. The objective in mind is, rather, the production of a steady and uniform effect of killed typhoid organisms on the defensive mechanism of the body, along with the production of a sustained stimulation of the adrenal cortex, which leads to the production of cortisone. The mobilized cortisone thereby interferes actively in inflammatory processes.

It differs from the other two methods in that patients are not exposed to untoward reactions, the life of the patient is not endangered, and the number of treatments required is less.

RESULTS

Although the number of patients (10) included in this report is admittedly small, the results obtained have been consistent and startling enough to justify one's considering this form of therapy of definite value. The reaction obtained in practically all instances was more or less uniform. Practically all patients had temperatures fluctuating between 99 and 101 F. These temperatures can hardly be considered hyperpyrexic. Hyperpyrexia is ordinarily understood to mean temperatures of higher than 104 F. The patients uniformly complained of a slight chill about one-half to one hour after the infusion was started. Throughout the infusion they more or less uniformly complained of general aching and malaise and of a slight to moderate headache. Occasionally the patient would complain of nausea, and a few vomited. Four of the patients complained of pain in the arm receiving the infusion. Most of these complaints were relieved by the intramuscular administration of 50 to 100 mg. of meperidine hydrochloride every four hours.

Of the 10 patients studied, two had acute iritis. One of these two patients (Case 2) received two rapid intravenous injections, with no noticeable improvement. After two infusions, given three days apart, the patient showed remarkable improvement and was considered clinically cured two weeks after the administration of the two treatments. The other patient showed a more spectacular response to this form of therapy. After one infusion the anterior chamber was free of cells, and the patient was considered clinically cured two days after the treatment had been administered. This patient was therefore discharged free of symptoms and well 48 hours after the therapy. The only other accessory treatment given to these two patients was instillation of 3% atropine sulfate solution into the affected eye three times a day.

Five of the patients treated had acute plastic iridocyclitis. One of these had a recurrence of the condition and was treated in both episodes with the method under discussion. All these patients showed a rather impressive, uniform response to the first infusion of typhoid vaccine administered. There was almost complete absorp-

tion of the plastic exudate. This permitted almost immediate visualization of the fundus. The disappearance of the plastic exudate was accompanied by restoration of vision to almost normal. At the end of 24 hours after the therapy, all these patients showed less ciliary flush and a notable reduction in the number of cells seen floating in the aqueous humor at the time of the patient's admission to the hospital. Concurrent with this change, the patients all volunteered the information that they experienced marked subjective improvement. This consisted in diminished photophobia, improved vision, diminution of pain in the involved eye, and a sensation of general well-being, probably due to the improvement in the condition of the eye. In this group of patients the visual acuity varied from as low as light perception only in one patient (Case 4) to 20/70 in another (Case 1). These patients became well on an average of 7½ days from the date of institution of this form of therapy.

Results Obtained in Patients with an Infusion Containing Typhoid Vaccine

Patient No.	Diagnosis	Vision Before Treatment	Vision After Treatment	No. of Infusions	Days in Hospital	Therapeutic Results
1 (1st hospitalization)	Acute plastic iridocyclitis, O. D.	20/70	20/40 —2 Atropinized	3	9	Cure
1 (2d hospitalization)	Acute plastic iridocyclitis, O. D.	.....	.....	3	23	Cure
2	Acute iritis, O. S.	20/25 —2	20/20 —2	2	23	Cure
3	Acute iritis, O. D.	20/15 —3	20/15 —1	1	2	Cure
4	Acute plastic iridocyclitis, O. D.	Light perception	20/20 —1	1	35	Cure
5	Vitreous hemorrhage, O. S.	No light perception	Counting fingers at 1 ft.	2	65	Improvement
6	Acute plastic iridocyclitis, O. S.	Counting fingers at 1 ft.	20/30 —1 Atropinized	3	32	Cure
7	Disciform keratitis, O. S.	12/200	20/200	3	39	Improvement
8	Juxtapapillary choroiditis, O. S.	20/30	20/20 +3 Atropinized	3	17	Much improvement
9	Acute plastic iridocyclitis, O. D.	20/100	20/50 Atropinized	1	6	Cure
10	Acute plastic iridocyclitis, O. S.	20/200	20/40 —2 Atropinized	2	10	Cure

The only other accessory treatment given these patients was instillation of 3% atropine solution to the involved eye three times a day.

One of the patients treated was a man with hyphema and massive vitreous hemorrhage following trauma to the eye. The hemorrhage in the vitreous was so massive that no reflex whatever could be obtained from the fundus. Two days after the last of two typhoid-vaccine infusions given three days apart, the blood in the anterior chamber and in the vitreous had been so absorbed that a reddish reflex was obtained from the fundus with the ophthalmoscope, and the lens, which was dislocated, was seen inferiorly in the vitreous. The visual acuity had increased from equivocal light perception to ability to count fingers at 1 ft. (25 cm.), The absorption of blood from the vitreous in this case was considered remarkable.

A patient with disciform keratitis (Case 7) involving the pupillary area of the cornea, with uncorrected vision of 12/200, received three intravenous infusions of typhoid vaccine three days apart. Examination of the eye under the slit lamp and biomicroscope the day after the last treatment showed considerable clearing of the affected part of the cornea. The patient volunteered that he could see much better.

Determination of the visual acuity at this time showed that the uncorrected vision had improved to 20/200. The patient stated that his eye had cleared considerably faster with this treatment than with the other therapy, which he received for a similar attack in the same eye three years previously.

The diagnosis in Case 8 was juxtapapillary choroiditis. The patient had had acute choroiditis in the same eye two years previously, at which time he was treated with single intravenous injections of typhoid vaccine and systemic administration of penicillin. He was discharged after one month, with vision improved.

The corrected visual acuity of the involved eye on this second admission was 20/30. The affected eye showed some vitreous haze. After three intravenous infusions of typhoid vaccine the vitreous opacities had absorbed considerably, and the exudative choroidal lesion was much improved. The corrected visual acuity had improved to 20/20 + 3. The patient was considered clinically cured after 17 days in the hospital.

The accompanying table shows the results obtained in this series of patients. It can be seen that the most favorable therapeutic results were obtained in cases of acute iritis and acute plastic iridocyclitis. For one patient with acute iritis the period of hospitalization was only two days, and for one with acute plastic iridocyclitis it was six days. Taken altogether, the average period of hospitalization for the patients with acute iritis and acute plastic iridocyclitis was 17.5 days.

Case 6 illustrates well the effect in a debilitated, undernourished patient with poor resistance, suffering with a chronic intestinal disease, who responded dramatically to this treatment and in whom no impairment in physical condition followed the therapy.

Results with other ocular conditions, as shown in the table, have not been as dramatic as with the acute nonspecific inflammations of the anterior uveal tract, but they are considered to be sufficiently good to warrant the use of typhoid-vaccine infusions in those conditions in which the ophthalmologist has little else to offer the patient.

COMMENT

The conventional method of using typhoid vaccine by the single-injection technique has been found to have certain disadvantages. These have been pointed out by Solomon and Somkin.[1] Chief among them are the unpredictable, and possibly dangerous, elevation of the temperature, the strenuous and rather prolonged period of chill, the necessity of injecting relatively large numbers of killed typhoid organisms at one time to insure a proper therapeutic response, and the important fact that after the injection the subsequent course of the reaction remains more or less out of control.

The reaction following the single injection of typhoid vaccine may be variable. While in some patients severe chills and fever occur, in others an equivalent dose may produce a very weak reaction. A severe reaction can be dangerous in elderly patients and in patients with heart disease.

By contrast, the technique of administering typhoid vaccine in an infusion presents the advantages that the chill is mild, and usually brought under control, or it can be relieved by meperidine hydrochloride. The elevation of temperature can also be controlled, and the physician can, to a certain extent, make it what he chooses by setting the rate of infusion at a specific rate. Most important of all, the method assures control of the reaction at any given moment. If the temperature

should attain a high level, a possibility which is not likely if the rates of infusion recommended are strictly adhered to, the infusion can be discontinued. A drop in temperature usually follows in a short time. If the temperature should remain elevated after the infusion is stopped, a saline solution or glucose infusion can be given intravenously, diluting the organisms in the blood and ameliorating the reaction. A drop in temperature follows the dilution of the organisms in the circulation. If a medical emergency should arise, emergency medication can be introduced into the infusion tube.

Although most of the patients I have treated are in the young age group, Curry and Shaw [2] have stated that a typhoid-vaccine infusion may be given without danger to elderly and debilitated patients and to persons with coronary arteriosclerosis.

Although most of the earlier authors seemed to think that shock or high fever was essential to insure an adequate therapeutic response with the single-injection technique of typhoid vaccine, the experience of my colleagues and myself with an infusion has been that equally good results are obtained in patients in whom the temperature response has been moderate. A few authors have had similar experiences while using the single injection of typhoid organisms. The so-called negative phase in the first procedure is short in time interval and increased in intensity, while in the second procedure it is prolonged in time interval and decreased in intensity. If, as has been pointed out by Potts, Johnson, Orchen and Goodman, cited by Dunphy,[3] the good therapeutic results following typhoid-vaccine injections are due to the stimulation of the adrenal cortex to produce cortisone through stress reactions acting on the pituitary gland, it is logical to assume that a steady, prolonged stimulus with slight to moderate fever is more desirable than an abrupt, short stimulus with high fever. The former would appear to be more physiologic. That this steady, prolonged stimulus is an important factor is borne out by the fact, already mentioned, that just as good therapeutic results were obtained in some of our patients whose temperature response was about 100 F. as in patients in whom it was 2 or 3 degrees (F.) higher. We are therefore of the opinion, from our limited experience, that the production of hyperpyrexia, either sustained or intermittent, is not essential to good therapeutic results, and we believe its elimination does away with one of the greatest hazards of typhoid-vaccine therapy.

A decided advantage of the method hereby described is in the number of treatments required to bring about a cure in a given case. In a severe case of iridocyclitis improvement may be spectacular after one treatment, and that may be all that is required. At the most, two or three such treatments may be required. Experience has shown that with the older procedure between 6 and 10 treatments may be required, with questionable results.

The period of hospitalization is also considerably shortened when typhoid vaccine is given in an intravenous infusion. This was clearly demonstrated in Case 2. The patient had an original attack of acute plastic iridocyclitis, for which he was treated with single injections of typhoid vaccine. His period of hospitalization was 34 days. A later recurrence was treated similarly, and the hospitalization period was 52 days. Third and fourth recurrences were treated with intravenous infusions containing typhoid vaccine. The period of hospitalization for the third recurrence was 9 days, and that for the fourth, 23 days.

3. Dunphy, E. B.: Ocular Therapeutic Principles and Practical Applications, Arch. Ophth. **44**:797, 1950.

The promptness of the resolution of the inflammatory products brought about by an infusion containing typhoid vaccine may be instrumental in preventing serious complications in cases of acute iridocyclitis and acute plastic iridocyclitis. An inflammation of the iris and the ciliary body which is permitted to linger may so impair the anatomy, function, and immunologic status of these organs that subsequent attacks of a similar nature become the lot of many of these patients. It is easy to visualize, therefore, that prompt clearing of the inflammatory products may spare both these organs pathologic changes which would prepare the soil, as it were, for further disease states of a similar or different nature.

We have observed frequently in the treatment of acute nonspecific inflammations of the anterior uveal tract that posterior synechiae that show a tendency to resist the ordinary therapeutic measures of instillation of cyclopegics and subconjunctival injections of various mydriatics and cyclopegics, alone or in combination, break dramatically when as little as one infusion containing typhoid vaccine is given with the concurrent use of cyclopegics. This, in our estimation, is of considerable importance, as it has often happened that an eye has been seriously compromised by the repeated unsuccessful attempts of the ophthalmologist to break these synechiae.

The only real disadvantage of this method is the length of the individual treatment. The administration of between 800 and 1,000 cc. of infusion at the suggested rate of 20 to 25 drops per minute takes between 8 to 12 hours. Some patients appear to dislike the idea of lying in bed for that length of time with their movements restricted.

CONCLUSIONS

The administration of typhoid vaccine in a saline infusion, as described, is a useful and efficient therapeutic procedure in ophthalmology.

A sustained or intermittent high fever is not necessary to produce good therapeutic results; therefore, hyperpyrexia does not appear to be essential to bring about successful treatments.

The number of treatments required for a given condition is considerably less with the continuous infusion than with the older, rapid injection.

The complications and dangers which are encountered with typhoid-vaccine therapy are better controlled with the infusion method.

The length of hospitalization is considerably diminished because a more rapid cure is effected.

SUMMARY

The historical development of a method for the intravenous administration of typhoid vaccine in the treatment of ophthalmic diseases is described.

The theories and probable mechanisms of the therapeutic action of typhoid vaccine administered intravenously are discussed.

The results obtained in treating a small number of patients with a continuous saline infusion containing killed typhoid organisms are described and tabulated.

The advantages of this method of treating certain ocular diseases over the older method of administering typhoid vaccine are discussed.

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OCULAR FINDINGS IN SCRUB TYPHUS

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SCRUB typhus, tsutsugamushi fever, or Japanese river fever, is a mite-borne acute febrile disease caused by the Rickettsia orientalis. It is endemic in Japan, China, Indo-China, Burma, Malaya, India, East Indies, New Guinea, Solomon Islands and Queensland, Australia. During World War II numerous cases were encountered among United States armed services personnel in Burma and Assam and in the New Guinea area. Scheie,[1] in 1945, published the first report on the ocular changes in scrub typhus. These ocular findings are particularly striking and may be of diagnostic aid in the early stages of the disease.

With the recent increased activity of the armed services in the Far-Pacific area, it would seem desirable to call further attention to the ocular findings in scrub typhus, as they have been described by Scheie in his Burma studies. It is the purpose of this paper to present evidence of similar ocular involvement in the quite-removed New Guinea area and to add support to the recognition of these ocular changes as a definite entity. This report is based on observations which I made while serving as ophthalmologist with the 4th General Hospital of the Medical Corps, United States Army, at Finschhafen, New Guinea.

REVIEW OF LITERATURE

Preliminary reports by Scheie appeared in April 1945 [1] and April 1946.[2] He placed emphasis on the edema of the disk and retina as the most characteristic feature of the retinopathy seen in scrub typhus. He also described the associated retinal hemorrhages and exudates.

Subsequent to these original reports by Scheie, a paper was published by Macaskill, in October, 1945,[3] and another by Donegan, in January, 1946,[4] in which ocular changes in scrub typhus were also described.

Macaskill's notes were based on observations on 70 patients who contracted scrub typhus in Assam. He recorded four patients with subjunctival hemorrhages, seven with engorged retinal veins, four with papilledema, and four with retinal

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1. Scheie, H. G.: Ocular Changes in Scrub Typhus, Bull. U. S. Army M. Dept. **87:** 37 (April) 1945.

2. Scheie, H. G.: Ocular Changes in Scrub Typhus, Bull. U. S. Army M. Dept. **5:** 423-427 (April) 1946.

3. Macaskill, J.: Some Ocular Complications of Scrub Typhus, Brit. J. Ophth. **29:** 537-540 (Oct.) 1945.

4. Donegan, E. A.: Ocular Findings in Tropical Typhus (Tsutsugamushi or Japanese River Fever), Brit. J. Ophth. **30:** 11-19 (Jan.) 1946.

hemorrhages. In one patient bilateral optic atrophy later developed. Donegan, in a survey of 101 patients with scrub typhus, reported 32 patients with vitreous haze overlying the nerve head and 17 patients with papilledema, which he interpreted as due to vascular disturbance.

The comprehensive thesis published by Scheie [5] in 1947, together with his earlier reports, constitutes the only record in the American literature of the ocular changes in scrub typhus. Scheie presented the ocular findings in 451 patients with this disease treated at the 20th General Hospital, in Burma. He examined at autopsy the eyes of nine of these patients and attempted to correlate the general systemic and the ocular findings.

The results of his clinical and ophthalmological examinations he summarized as follows:

A. External changes: (1) conjunctival hyperemia, 38%; (2) subconjunctival hemorrhages, 6.4%; (3) ecchymosis of the eyelids, 1%; (4) eschar on eyelid, 0.5%; (5) fixation nystagmus, 0.5%.

B. Intraocular changes: (1) engorgement of retinal veins, 67%; (2) retinal edema, 36%; (3) retinal hemorrhages, 6.6%; (4) exudates, 4.9%; (5) uveitis, 1.3%; (6) vitreous opacities, 4.6%.

The most significant of Scheie's ophthalmoscopic findings was the presence of edema of the nerve head and adjacent portion of the retina, and this constituted the cardinal feature of what he has termed "scrub-typhus retinopathy." The advent of the edema he found to be often predictable on the basis of venous engorgement, and this usually occurred in the second or third week of the disease. The edema often persisted for many weeks, well into the period of convalescence. The elevation of the nerve head he found to be never more than 2½ D., and seldom more than 1½ D. Scheie recorded in these patients occasional slight enlargement of the blind spots.

Neither Macaskill nor Donegan clearly emphasized edema of the nerve head and adjacent retina as the significant feature of the retinopathy seen in scrub typhus. Donegan mentioned vitreous haze overlying the nerve head as his commonest finding; this was not borne out by Scheie's observation.

SCRUB TYPHUS IN THE NEW GUINEA AREA

During 42 months' service in the Southwest-Pacific area, several hundred patients with scrub typhus were treated at the 4th General Hospital. The majority of these patients seen during the earlier period of the war had no signs or symptoms of ocular involvement. However, many of them were convalescent, and at that time there was no apparent indication for a comprehensive ophthalmological investigation.

In August and September, 1944, however, some 150 patients with scrub typhus were admitted to this hospital, largely from an outbreak of the disease at Sansapor, in Netherlands New Guinea, and within this group a variety of ocular lesions were encountered. These patients were studied in some detail, as at that time no reports on involvement of the eyes in this condition were found in the literature.

5. Scheie, H. G.: Ocular Changes in Scrub Typhus: A Study of 451 Patients, Tr. Am. Ophth. Soc. **45**: 637-677, 1947.

GENERAL FEATURES OF THE DISEASE

Scrub typhus is a mite-borne rickettsial disease which was found prevalent in the New Guinea area and adjacent Pacific Islands, from whence the patients were drawn. The mite was located in the tall cunai grass present in cleared or open spaces in the jungle; it is parasitic to native tropical rodents. The bite of this infected mite develops into a small primary necrotic ulcer, or eschar, about 0.5 cm. in diameter. The onset of the disease is characterized by headache, dizziness, malaise, and a rapid rise in temperature. The lymph nodes draining the region of the primary eschar become swollen and tender. A macular rash may appear after about one week of fever. Delirium and a high degree of prostration are frequent during the acute phase of the disease. The temperature usually falls by lysis after about two weeks. Deafness is a common complication. Mortality figures reported in different localities vary from 5 to 60%, and in one small outbreak at Finschhafen, New Guinea, the mortality was more than 80%. Postmortem studies showed perivascular infiltration as the commonest histopathological lesion.

REPORT OF CASES

The following cases are presented to illustrate the various types of ocular lesions encountered in scrub typhus. In the discussion to follow, the relative incidence of some of these findings is indicated, but no attempt is made to express this on a percentage basis, as an insufficient number of consecutive cases were surveyed to permit such an analysis to be significant. The first two cases are reported in particular detail because of the extensive and varied nature of the ocular involvement.

CASE 1.—F. C., an infantry private aged 21, noticed increasing redness and swelling of the outer portion of the right upper lid on Aug. 5, 1944, while on duty at Sansapor, Netherlands New Guinea. He also had a tender lump in front of his right ear. On Aug. 8 he had onset of headache, malaise, chills, and fever. With a temperature of 104 F., he was admitted to the hospital where examination revealed an eschar of the right upper eyelid and enlargement and tenderness of the right preauricular and submaxillary lymph nodes. There was also an eschar on the right side of the scrotum, with right inguinal lymphadenopathy. No rash was present.

He maintained an elevation of temperature in the vicinity of 104 F. for 2½ weeks and was acutely ill and delirious, requiring intravenous administration of plasma and parenteral use of fluids. As the fever subsided, the patient's general condition slowly improved.

Approximately three weeks after onset of the disease, the patient first complained of aching pain in both eyes and increasing photophobia, tearing, and blurring of vision. A detailed ophthalmologic examination was done on Sept. 13. Vision was 20/30 in each eye, unimproved by lenses. There was tenderness on palpation of each eye, but intraocular tension was normal. The temporal portion of the right upper lid was red and moderately swollen, and there was still a healing ulcerative lesion near the lash border, with absence of cilia for a space of 3 mm. The preauricular lymph nodes were still palpable and slightly tender. Circumcorneal and conjunctival injection was apparent in each eye. The irises were edematous, and the pupils were small and irregular, with a posterior synechia in each eye. Examination with the slit-lamp and corneal microscope showed many inflammatory cells in the anterior chambers with fine deposits on the posterior corneal surfaces and the anterior lens capsules. There was slight diffuse haziness of the vitreous bodies. Ophthalmoscopic examination disclosed a rather pale, watery edema of the nerve heads, whose margins were blurred, but there was no measurable elevation. The veins were somewhat engorged, and the retina was edematous, particularly adjacent to the optic nerve, but no hemorrhages or exudates were seen.

Visual fields on Sept. 19 revealed normal peripheral limits, but the blind spots were much enlarged, measuring 9 by 13 degrees in the right eye and 10 by 13 degrees in the left eye (0.5=degree white test object at 33 cm.).

Neither the blood serum nor the spinal fluid agglutinated with OXK. Lumbar puncture disclosed no increase in pressure; the spinal fluid was grossly clear; the cell count, 10 lymphocytes per cubic millimeter, and the spinal fluid proteins, 27 mg. per 100 cc.

Ophthalmological treatments included use of atropine and hot compresses, and posterior synechiae were broken without difficulty. After four weeks' therapy, the ciliary injection had disappeared, and there were no inflammatory cells in the anterior chambers. The edema of the optic nerves and retinas slowly subsided, and at the end of three months the fundi were of normal appearance.

During this period of convalescence the blind spots decreased in size as the edema of the nerve heads diminished; on Oct. 4, measurements were 8 by 12 degrees in the right eye and 8 by 11 degrees in the left eye; on Nov. 18, 7 by 9 degrees in each eye; on Dec. 14, 5.5 by 7.5 degrees in the right eye and 6.5 by 8 degrees in the left eye. Otherwise, there were no demonstrable defects of the central fields, and the peripheral limits remained normal.

There was no evidence of recurrent intraocular inflammation during the three months' observation, but there was still moderate conjunctival injection, and the patient had some persistent irritation, tearing, and photophobia. He also complained of ocular fatigue and bitemporal headaches. Visual acuity had improved to 20/20 in each eye, but the amplitude of accommodation was only 4 D.

Case 2.—R. F., an infantry private aged 29, experienced dizziness, weakness, malaise, chills, and fever on Aug. 13, 1944, while on duty at Sansapor, Netherlands New Guinea. There were no initial ocular complaints. He was hospitalized and found to have an eschar on the left anterior chest wall, with left axillary lymphadenopathy; no rash was present.

The patient was acutely ill, disoriented, and delirious for 2½ weeks, the temperature ranging to 104 F. The fever then gradually subsided, and his general condition slowly improved.

It was not until Sept. 5, on the 22d day of illness, that the patient first complained of pain in both eyes, with photophobia, tearing, and marked blurring of vision.

A detailed ophthalmological study was made on Sept. 16, and corrected vision was found to be 20/40— in the right eye and 20/40— in the left eye. The eyeballs were tender, but intraocular tension was normal to palpation. There was pronounced ciliary and conjunctival injection; the irises were edematous and the pupils, small and irregular, with posterior synechia present in each eye. With slit-lamp and corneal microscope, many inflammatory cells were seen in the anterior chambers, and there were numerous deposits on the posterior surfaces of the cornea and the anterior capsules of the lens in both eyes. Slight diffuse haziness was present in the vitreous bodies. The optic nerves were poorly defined, grossly edematous, and elevated 1 D. in the right eye and 2 D. in the left eye. The retinal veins were moderately engorged. There was a watery edema of the retinas, particularly adjacent to the optic nerves; and in each eye there was a superficial, flame-shaped hemorrhage near the disk. In the left eye was also an irregular patch of fresh exudate of the cotton-wool type.

Determination of the visual fields disclosed normal peripheral limits, but there was pronounced enlargement of the blind spots; they measured 8 by 11 degrees in the right eye and 9 by 14 degrees in the left eye (0.5-degree white test object at 33 cm.).

Agglutination tests of the blood serum with the OXK strain were reported as positive only in a 1:20 dilution. Lumbar puncture showed no increase in spinal fluid pressure, and the dynamic factors were normal. The spinal fluid was grossly clear, and there were no cells; spinal fluid proteins measured 58 mg. per 100 cc. Agglutination tests of the spinal fluid with OXK were negative.

Treatment of the eyes included use of atropine and hot compresses, and posterior synechiae were broken with moderate difficulty. The circumcorneal injection gradually subsided and in six weeks no cells were seen in the anterior chamber and the vitreous was clear in both eyes. By this time the retinal hemorrhages and exudates had been completely absorbed. However, the edema of the optic nerves and retinas, though diminished, was still present at the end of three months.

During this period of convalescence the peripheral visual fields remained normal. The blind spots decreased in size with the reduction in edema of the nerve heads: On Oct. 4, measurements were 7.5 by 11 degrees in the right eye and 8 by 12.5 degrees in the left eye; and by Nov. 22, 6.5 by 8 degrees in the right eye and 6.5 by 9 degrees in the left eye. However, in the left eye a small absolute scotoma, 2.5 degrees in diameter, was then demonstrable 3 degrees temporal to the fixation point. Corrected vision had improved to 20/20 in each eye.

Although there was no demonstrable iridocyclitis at the end of six weeks, moderate conjunctival injection persisted, and the patient still had irritation, tearing, and photophobia. He

also complained of dull bifrontal and retrobulbar headaches, ocular fatigue, and blurring of near vision. Visual acuity with correction had improved to 20/20 in each eye, but amplitude of accommodation was reduced to 5 D.

CASE 3.—D. S., an infantry private aged 19, had onset of headaches, backache, malaise, chills, and fever on Aug. 13, 1944, while on duty at Sansapor, Netherlands New Guinea. He complained particularly of pain in the eyeballs and pain on movement of the eyes and had moderate photophobia. On hospitalization he was found to have an eschar on the inner aspect of the left thigh and left inguinal adenopathy with tenderness. His temperature ranged up to 105 F. for nine days, after which the fever gradually subsided.

Two weeks after onset of the disease he first noticed increasing blurring of vision, especially in his right eye. This blurring was present at all distances and seemed to involve primarily the central fields. The patient stated that his vision had been normal in each eye prior to the attack of scrub typhus.

On Oct. 3, ophthalmological examination showed visual acuity of 2/200 (eccentric) in the right eye and 20/30 in the left eye. The extraocular-muscle function was normal. External examination, including that with the slit-lamp and corneal microscope, revealed nothing of significance; there was no evidence of the inflammation of the anterior segment, and the ocular media were clear. There was marked watery edema of both nerve heads and the adjoining retinas; the disk was elevated 1½ D. in each eye. The veins were moderately engorged, but no hemorrhages or exudates were seen.

Visual fields revealed approximately normal peripheral limits, but in the right eye there was a large central scotoma, including the point of fixation and measuring 23 by 30 degrees (0.5-degree white test object at 33 cm.). In the left eye was a larger scotoma, which was paracentral, approaching to within 8 degrees of fixation from the temporal and superior aspects and measuring 28 by 45 degrees.

Unfortunately, the patient was not available for subsequent examinations.

CASE 4.—L. G., an Army private aged 30, had onset of malaise, chills and fever and stiffness of the neck while on duty at Aitape, New Guinea, on July 1, 1944. He experienced blurred vision and photophobia; he also had weakness of the arms and legs, paresthesias, and fibrillary twitching. Eschars were present on the left side of the chest and on the right elbow. His course was particularly stormy; he ran a high fever and was delirious for more than three weeks.

Ophthalmoscopic examination showed watery edema and hyperemia of each nerve head and adjacent retina; there were pronounced blurring of the disk margins and engorgement of the retinal veins. No hemorrhages or exudates were seen.

During the acute phase of his illness no more detailed ophthalmological investigation was carried out, owing to his general debility and disorientation.

Eight weeks after onset of the disease the external examination was noncontributory, and the ocular media were clear. Study of the fundi still showed hyperemia of both nerve heads, with residual edema blurring the disk margins and extending into the adjacent retina. The retinal veins were no longer engorged, and again there was no hemorrhage or exudate. Visual fields on Sept. 12 revealed definite enlargement of the blind spots, which measured 7.5 by 10 degrees in the right eye and 7.5 by 10 degrees in the left eye. These blind spots were again checked on Oct. 5, 1944, when they measured 6.5 by 8 degrees in the right eye and 6.5 by 9 degrees in the left eye. By this time there had been a definite decrease in the apparent edema of the nerve heads.

CASE 5.—S. A., an infantry sergeant aged 28, had onset of headache, backache, malaise, chills, and fever on Aug. 15, 1944, while on duty at Sansapor, Netherlands New Guinea.

During this initial phase he also complained of pain in the eyeballs, aggravated particularly by movement of the eyes, and moderate generalized blurring of vision, with irritation, photophobia, tearing, and conjunctival discharge.

On hospitalization, an eschar was found in the left groin, and there was left inguinal lymphadenopathy with tenderness. Though not severely prostrated, he was acutely ill, with a temperature ranging to 103.5 F., for 10 days. As the fever subsided, his general condition began to improve, and initial ocular complaints disappeared, although he was still conscious of slight visual impairment.

Examination on Sept. 23, 1944, showed vision of 20/70, corrected to 20/30, in each eye. External examination, including study with the slit-lamp and corneal microscope, revealed no evidence of intraocular inflammation. The ocular media were clear. Ophthalmoscopic examination disclosed edema of the nerve head and adjacent retina in both eyes; the disks were elevated about 1 D., and margins were poorly defined. The retinal veins were moderately engorged, but no hemorrhages or exudates were seen.

Visual fields revealed approximately normal peripheral limits, but blind spots were significantly enlarged, measuring 9 by 12 degrees in the right eye and 8 by 10.5 degrees in the left eye (0.5-degree white test object at 33 cm.). Determination of the fields, repeated two weeks later, showed reduction in size of the blind spots, which measured 8 by 10 degrees in the right eye and 7 by 9 degrees in the left eye. During this interval the edema of the nerve heads had subsided perceptibly.

Case 6.—A. B., an infantry corporal aged 26, had onset of headache, backache, malaise, chills, and fever on Aug. 14, 1944, while on duty at Sansapor, Netherlands New Guinea. He also complained of swelling, redness, and tenderness of the outer portion of the left lower lid. There were intense photophobia and pain in the eyes, aggravated by ocular movements. There was transient blurring of the left eye, as though by a veil.

The patient was hospitalized on Aug. 18, 1944, with a temperature of 104 F. An eschar was present on the left lower eyelid, and there was submaxillary and preauricular adenopathy. Another eschar was found on the right forearm. He ran a sustained elevation of temperature to 104 F. for two weeks and was acutely ill, but not prostrated.

Ophthalmological examination during convalescence, on Sept. 13, showed visual acuity of 20/20 in each eye. There were residual redness, swelling, and absence of lashes on the left lower lid, at the site of the healing eschar. Examination with the slit-lamp microscope revealed no evidence of iritis, and the ocular media were clear. Funduscopic study disclosed hyperemia of the disks and only moderate watery edema of the nerve heads and surrounding retina. There was some fulness of the retinal veins.

Repeated studies of the visual field revealed moderate, but definite, peripheral constriction, i. e., 70 degrees temporally and 40 degrees nasally, in each eye. The blind spots were somewhat large, measuring 9 by 11 degrees in the right eye and 8.5 by 10 degrees in the left eye. This patient, however, showed a surrounding area of relative scotoma, measuring 18 by 20 degrees in the right eye and 12 by 14 degrees in the left eye. On Oct. 6, 1944, the absolute blind spots had decreased in size to 7 by 9.5 degrees in each eye.

Case 7.—D. B., an infantry corporal aged 21, experienced bitemporal headache, chills, and fever on Aug. 13, 1944, while on duty at Sansapor, Netherlands New Guinea. He complained of pain in the eyeballs, aggravated by movement of the eyes, and photophobia. Eschars were found on the scrotum and in the left axilla, and there was regional lymphadenopathy. He was hospitalized, with temperatures ranging up to 104 F., 11 days, and during this acute phase he continued to complain of aching discomfort in his eyeballs, with burning, tearing, and photophobia.

After the fever subsided, ophthalmological examination revealed visual acuity of 20/20 in each eye. The left pupil was slightly smaller than the right, but both were regular and reacted normally to light and in accommodation. The slit-lamp microscope disclosed no evidence of anterior-segment inflammation. The vitreous was clear. The fundus of the right eye disclosed moderate hyperemia of the disk, with slight blurring of the nasal margin but no appreciable edema of the adjacent retina. The left nerve head was definitely hyperemic and edematous, and there was marked blurring of the disk borders, with the edema spreading into the retina. No hemorrhages or exudates were seen.

On Oct. 5, 1944, the peripheral visual fields were normal, but the blind spots were moderately enlarged, measuring 7 by 9 degrees in the right eye and 8 by 11 degrees in the left eye. Three weeks later the blind spots measured 6.5 by 7 degrees in the right eye and 6 by 8 degrees in the left eye.

Case 8.—F. S., an infantry private aged 31, had onset of headache, chills, and fever on Aug. 1, 1944, while on duty at Biak, Netherlands New Guinea. He also experienced pain on movement of the eyeballs and photophobia. He was hospitalized, with a temperature ranging up to 104 F., for 2½ weeks. No eschar was found, and there was no rash. As the temperature

began to subside, he noticed pronounced blurring of vision in the right eye. He stated that vision had been 20/20 in each eye on induction into the Army.

Ophthalmological investigation, on Sept. 6, 1944, showed the corrected visual acuity to be 20/100 in the right eye and 20/20 in the left eye. External examination revealed moderate conjunctival injection but no evidence of iridocyclitis. There were no cells in the anterior chamber of either eye, and no deposits on the cornea or lens. The vitreous of the right eye was diffusely hazy; in addition, there were many large floating opacities, particularly in the lower portion. There was also a streamer-like opacity which came forward from the disk and had the appearance of an anomalous retinal vessel. The fundus detail was largely obscured by the vitreous opacities, which under the slit-lamp microscope were found to be composed of red blood cells. Examination of the fundus of the left eye disclosed only moderate hyperemia of the nerve head, with no appreciable edema. No hemorrhages or exudates were seen in the left eye.

CASE 9.—J. V., an infantry private aged 24, had onset of severe headache, backache, malaise, chills, and fever on Aug. 10, 1944, while on duty at Sansapor, Netherlands New Guinea. He experienced pain in the eyes, aggravated by motion of the eyeballs. There was some redness but no conjunctival discharge. Vision in the right eye was blurred.

The patient was found to have an eschar in the right axilla, with enlargement of the axillary lymph nodes. He was acutely ill and prostrated for 19 days, with temperatures up to 104 F.

In the third week of illness he noticed increasing blurring of vision, particularly in the right eye, with associated pain, tenderness, and photophobia.

On Sept. 23, he was studied in the eye clinic. Corrected visual acuity was then 20/30 in the right eye and 20/20 in the left eye. External examination revealed no gross abnormality, but slit-lamp microscopy of the right eye showed many inflammatory deposits on the posterior surface of the cornea. No cells were present in either anterior chamber. The lens and vitreous were clear in each eye.

The optic nerve heads were slightly edematous in appearance, with moderate hyperemia and some blurring of the disk margins. In the right retina there were two small patches of soft exudates near the nerve head. No hemorrhages were seen in either eye.

There was apparently a slight constriction of the peripheral visual fields, which measured 70 degrees temporally and 35 degrees nasally in the right eye and 70 degrees temporally and 40 degrees nasally in the left eye. The blind spots were moderately enlarged, measuring 7.5 by 9.5 degrees in the right eye and 7.5 by 10 degrees in the left eye.

CASE 10.—H. D., an infantry staff sergeant aged 25, had onset of headaches, malaise, and fever while on duty at Sansapor, Netherlands New Guinea. There were redness and conjunctival discharge in each eye. An eschar was present at the inner angle of the right lower eyelid, with adjacent swelling and tenderness. There was lymphadenopathy in the submaxillary and cervical chains on the right side.

The patient was acutely and seriously ill for 18 days, with elevations of temperature to 104 F. He became deaf in the right ear. The serum agglutinated with OXK in a dilution 1:320.

An ophthalmological survey, done Sept. 23, showed visual acuity of 20/20 in each eye. There was a fresh scar on the skin at the site of the eschar of the lower lid near the inner canthus of the right eye. There was slight conjunctival hyperemia, but the slit-lamp examination was entirely noncontributory. The nerve heads were normal in appearance, and no hemorrhages or exudates were seen.

The visual fields revealed normal limits centrally and peripherally, the blind spots measuring 6 by 8 degrees in each eye.

OCULAR SYMPTOMS IN SCRUB TYPHUS

There were no ocular complaints which were uniformly encountered. However, in about two-thirds of the patients there was pain in the eyeballs, which was aggravated by movement of the eyes and was most pronounced during the initial stages of the disease. Photophobia, irritation, tearing, and moderate conjunctival discharge were somewhat less frequently experienced. These symptoms were often present in patients in whom no significant ocular signs attributable to scrub typhus ever developed.

Slight blurring of vision was a rather frequent complaint during the febrile stage, but many of the patients so affected were so seriously ill that their estimates were not reliable. The occasional instance of serious visual loss did not usually develop until the end of the second or third week, after the fever had begun to subside; then ocular pain, tenderness, severe photophobia, and tearing were usually associated. In the infrequent cases in which the mite had bitten the eyelids, there were painful swelling of the lid tissues and preauricular adenopathy with tenderness.

OBJECTIVE FINDINGS

For convenience, the objective findings may be divided into three groups according to the structures chiefly affected: (1) adnexa and external tissues of the eye; (2) iris and anterior segment of the globe proper, and (3) posterior segment, particularly the retina and optic nerve. A single patient may show involvement in all three categories.

The most extensive lesion of the adnexa occurs when the mite chances to bite the eyelids, and three such instances were found in this series of 150 patients under consideration. The eschar, or small necrotic ulcer, develops at the site of the bite, and this is surrounded by a dark-red areola. In the loose tissue of the lid the swelling and reaction are considerable. With the ultimate healing of the eschar there may be scarring, with loss of cilia where the lash border chances to be involved. Preauricular or submaxillary lymphadenopathy with tenderness accompanies the eschar. Again, this primary lesion is well established before the onset of the febrile phase, but the necrotic ulcer may persist well into the period of convalescence.

The commonest finding during the acute fever is injection of the conjunctiva, often with some conjunctival discharge. This is not unlike the picture in other prostrating febrile diseases. Subconjunctival hemorrhages of variable extent are occasionally encountered.

Two cases of rather severe bilateral iridocyclitis are reported. Among the patients examined there were two with unilateral iritis. During the acute stage, the prostration is so marked as to make study with the slit-lamp and corneal microscope impractical. However, in these two instances of bilateral iridocyclitis the ocular changes did not develop until the fever was subsiding, after the end of the third week. The inflammation was only moderately severe, and the posterior synechiae were broken away without undue difficulty. The deposits on the posterior surface of the corneal and posterior lens capsule were rather fine and not readily visible without the slit-lamp and corneal microscope. There was associated diffuse haziness of the vitreous, but no large opacities were visualized. There was no involvement of the lens substance.

The iridocyclitis responded only slowly to treatment, requiring from four- to six-weeks' therapy before all inflammatory cells had disappeared from the anterior chambers. However, at the end of three months there were still irritation and residual photophobia.

The most frequent manifestation of involvement of the posterior segment of the globe was edema of the optic nerve and adjacent retina. This gives a rather watery appearance to the nerve head, whose margins are indistinct. The edema spreads into the adjacent retina, with no definite line of demarcation. The nerve heads are usually not appreciably raised, but in some instances there may be an elevation of 1 to 2 D. There is usually an associated engorgement of the retinal veins, which may be pronounced. In the two cases of bilateral iridocyclitis there was also marked

edema of the optic nerves, but in most patients with retinal edema there was no evidence of associated iridocyclitis.

Occasionally small superficial flame-shaped retinal hemorrhages are seen, oftenest in the vicinity of the optic nerve and macula; somewhat less commonly small cotton-wool exudates are encountered. These hemorrhages and exudates are more frequent during the acute febrile phase, but occasionally persist several weeks. In one case massive fresh hemorrhage into the vitreous was encountered, which apparently had its origin in an anomalous retinal vascular structure.

The commonest visual-field change was that of enlargement of the blind spots, which was present in patients with edema of the nerve head and was roughly proportional to the degree of edema present. As the ophthalmoscopic appearance improved, there was a corresponding decrease in the size of the physiologic blind spots. In most cases the optic-nerve edema subsided within a few weeks, leaving no apparent alteration in the appearance of the nerve head or in the visual field.

Additional field changes are summarized as follows: A small absolute paracentral scotoma, measuring 2.5 degrees in diameter, was found in one case. In another a large central scotoma involved the point of fixation in the right eye, and a similar, but paracentral, scotoma was found in the left eye. In addition, there was moderate peripheral constriction of the visual fields in two other patients.

COMMENT

The nature of the optic-nerve involvement poses an interesting problem. The appearance is not that of papilledema due to increased intracranial pressure, and in the two cases in which lumbar puncture was done the cerebrospinal fluid pressure was normal.

It is particularly significant that Scheie was able to correlate the clinical findings with postmortem pathological sections of the eyes in nine cases. The clinical findings of edema of the nerve head and retina and engorgement of the retinal veins were confirmed in the pathological sections. Scheie described the pathological changes as consisting predominantly of posterior choroiditis, evidenced by mononuclear round-cell infiltration, and expressed the belief that these pathological changes explain the edema of the nerve head and retina, and that a similar process in the anterior uveal tract accounts for the iridocyclitis.

In this series, enlargement of the blind spots was uniformly encountered in patients with edema of the nerve heads, whereas Scheie reported only occasional increase in size of the physiological blind spots. It is also interesting that one patient had large central and paracentral scotomas, suggesting involvement of the optic nerve proper, in addition to the obvious edema of the nerve head and retina.

SUMMARY

It has been the purpose of this paper to report ocular changes in scrub typhus, as studied in the New Guinea area, and to add support to the recognition of these ocular signs as a significant entity. The most frequent and characteristic manifestation of ocular involvement is edema of the optic nerve and retina. There is an associated enlargement of the blind spots, which is roughly proportional to the degree of edema seen with the ophthalmoscope. This edema of the papilla and surrounding retina constitutes the cardinal feature of what has been termed "scrub-typhus retinopathy."

DACRYOCYSTORHINOSTOMY IN INFANTS AND CHILDREN

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MILWAUKEE

DACRYOCYSTORHINOSTOMY in adults has become the procedure of choice for the cure of chronic dacryocystitis, mucocele, and epiphora. The marked trend from dacryocystectomy to dacryocystorhinostomy is due to the high percentage of successes of the latter in relieving the purulent discharge and tearing. There is apparently no reason for any other procedure being performed for these conditions so long as at least one canaliculus is patent. Age is not a contraindication. Rychener [1] has employed this operation on patients from the age of 18 months to 72 years. I have performed the operation for the relief of recurrent acute dacryocystitis in a patient 80 years of age. The need for dacryocystorhinostomy in young children has been mentioned only in the recent literature. Redmond [2] reported its use bilaterally in a 3-year-old child, with success, and Aalde,[3] in a 3-month-old boy. Simpson [4] successfully performed dacryocystorhinostomy on a 7-year-old boy for bilateral congenital fistula of the lacrimal duct. He emphasized that fistulas from the frontal sinuses always occur above the internal canthal ligament, and the lacrimal fistulas, below. On the other hand, in 1935 Riser [5] reported the necessity of doing a dacryocystectomy on four patients, aged 2 to 8 years, for acquired dacryostenosis with accompanying dacryocystitis. In 1941 Judge [6] mentioned two patients observed during the first year of life in whom extirpation of the sac was necessary. In these children the disease had started shortly post partum but had been neglected or improperly treated.

The incidence of acute dacryocystitis shortly after birth must indeed be rare. Riser [5] reported a case of bilateral phlegmonous inflammation occurring at less than 2 months of age in which recovery followed incision of the abscess and subsequent probing. In Redmond's [2] case an abscess of the left lacrimal sac developed at the age of 3 weeks and eventually required dacryocystorhinostomy. It is rare that chronic dacryocystitis or obstruction of the lacrimal duct in an infant cannot be relieved. Probing of the nasolacrimal duct is highly successful, as shown by

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Cassady,[7] Koke,[8] and Guerry and Kendig.[9] Rychener [1] stated that probing should be used in the first few weeks or months of life, for a delay may result in acute dacryocystitis with all its complications, including osteomyelitis of the maxilla, which he has personally witnessed. Acquired dacryocystitis in young children is rather uncommon. However, Riser [5] described a series of 12 cases of the acquired form, with an average age of onset of 4.5 years. The etiologic factors varied: Scarlet fever was implicated in four cases; trauma, in three cases; respiratory-tract infections, in two cases; foreign body in the nose, in one case, and an unknown cause, in two cases. In none of the cases was cure effected with conservative treatment, or with probing or irrigation. In three cases recovery from an acute phlegmon was effected. In six cases a major surgical procedure on the lacrimal sac was performed or advised. In these cases the course differed strikingly from the benign course in most of the cases of congenital obstruction of the lacrimal duct.

The following cases are reported to illustrate the results of dacryocystorhinostomy in young children and infants. The indication for operation was different in each case. The surgical procedure was that popularized by Dupuy-Dutemps.[10] The external approach was used. A straight-line incision midway between the canthus and the bridge of the nose was first made, as suggested by Hogan.[11] The incision was carried down to the nasal bones, and the periosteum was incised and elevated from the bone and lacrimal crest. The lacrimal sac was displaced temporally, exposing the lacrimal fossa, and the lacrimal bone posteriorly. Behind the posterior crest a perforation was made in the lacrimal bone with a strabismus hook, large enough to permit use of a small Kerrison punch. The opening was enlarged anteriorly and superiorly to about 1.5 cm. in diameter. This usually included part of the anterior lacrimal crest. The nasal mucosa was identified; any ethmoid cells encountered were exenterated with a curet. All bleeding was controlled by pressure, packing, or the use of gelfoam.® The mucosa of the nose and lacrimal sac was so incised as to fashion an anterior and a posterior flap from each area, and the anterior and posterior flaps were sutured together by two interrupted surgical gut sutures. When it was found that the nasal mucosa had been traumatized or was too fragile, enough usually was found to form an anterior flap to be sutured to the anterior flap of the lacrimal sac. The posterior flap of the lacrimal sac then was excised. The skin and subcutaneous tissues were closed in layers.

REPORT OF CASES

CASE 1.—D. V., a 29-month-old girl, was first examined on July 27, 1948. The date of birth was Feb. 21, 1946. The history obtained from the parents revealed that the infant, at the age of 2 weeks, had acute dacryocystitis, first on the right side and then, within a few days, on the left side. An incision for drainage of the abscess was performed bilaterally at home. This was followed by profuse discharge. The drainage from the incision on the left cleared 10 months

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9. Guerry, DuPont, III, and Kendig, E. L., Jr.: Congenital Impatency of Nasolacrimal Duct, Arch. Ophth. **39**:193 (Feb.) 1948.

10. Dupuy-Dutemps, and Bourguet: Procédé plastique de dacryocysto-rhinostomie et ses résultats, Ann. ocul. **158**:241-261 (Oct.) 1921.

11. Hogan, M. J.: Dacryocystorhinostomy, Tr. Am. Acad. Ophth. **52**:600-612 (July-Aug.) 1948.

later. The incision on the right, however, persisted as a lacrimal fistula. Treatment in the meantime consisted in expression of the purulent material from both lacrimal sacs and the instillation of penicillin ointment. Her twin sister, at the age of 6 weeks, had onset of tearing and discharge from both eyes. This was relieved by two probings of the nasolacrimal duct.

Examination revealed a lacrimal fistula in the center of a rather wide scar in the area of the right lacrimal sac below the internal canthal ligament. Purulent material was expressed from the lower punctum, but a greater amount exuded from the fistula. On the left a healed scar could be seen, over the lacrimal sac, and purulent material was easily expressed through

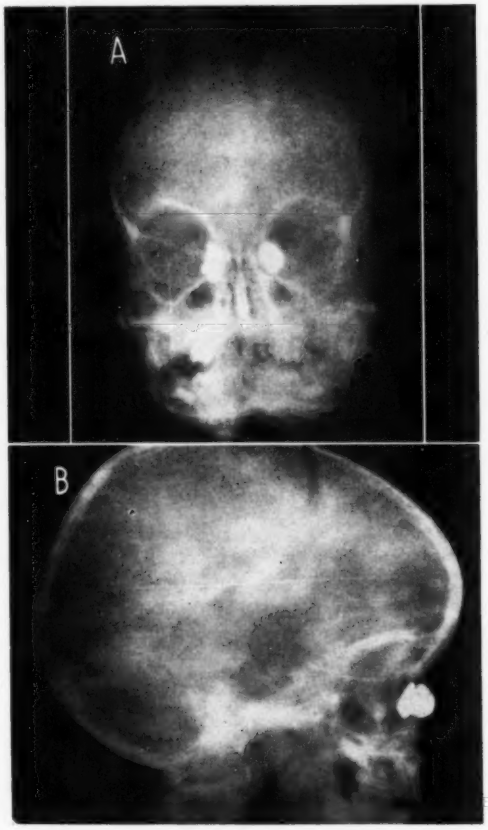

Fig. 1 (Case 1).—*A*, pronounced dilatation, following injection of iodized oil U. S. P. into both lacrimal sacs. *B*, lateral view showing bilateral filling of both lacrimal sacs with iodized oil. The anterior bulging of the filled sacs is illustrated.

the upper punctum. There were no other ocular defects. X-ray studies showed clouding of the ethmoid and maxillary sinuses. There was no osteomyelitis or bony destruction. Smears from the purulent secretion revealed no pathogens except an occasional yeast form. Many polymorphonuclear leucocytes were present. Culture yielded no growth. Examination of the nose showed no discharge. Injection of iodized oil U. S. P. through the lower punctum showed prominent enlargement of the lacrimal sacs in roentgenograms. The left sac measured 1.5 by 1 cm., and the right, 2 by 0.8 cm. On March 3, 1949, a right dacryocystorhinostomy was performed, with the incision made nasal to the fistulous scar. After a large enough opening was

made in the medial bony wall, satisfactory mucosal flaps from the nose and lacrimal sac were fashioned. Two surgical gut sutures were used to connect the two anterior flaps and the two posterior flaps. On July 14, 1949, a left dacryocystorhinostomy was performed. Only the anterior flaps could be fashioned from the mucosa. The remnants of the posterior flaps were cut off flush with the bony opening, and the anterior flaps were connected with two interrupted surgical gut sutures. The tearing and discharge after each procedure completely disappeared. The right lacrimal fistula closed spontaneously. A drop of fluorescein in each conjunctival sac almost immediately appeared in the nose. On Nov. 15, 1951, both eyes were dry. There had been no tearing or discharge since the operation. The scars were barely perceptible.

CASE 2.—S. F., a boy born on May 24, 1942, had a history of birth trauma, with repeated convulsions in infancy, and of alternating esotropia, for which he had been treated since Feb. 4, 1946. It was noted at this time that he was mentally defective. The refractive error was as follows: Right eye: +1.50 sph. $\bigcirc$ +2.00 cyl., axis $\times$ 90; left eye: +2.00 syp. $\bigcirc$ +2.50 cyl., axis $\times$ 90. He was wearing a full correction, which reduced his esotropia to 4$\triangle$. On July 21, 1948, he was seen for tearing of both eyes, purulent discharge, and agglutination of the lids. The conjunctivitis disappeared under treatment, but the tearing continued. He was not seen again until Jan. 30, 1950, but both eyes had continued to discharge and tear during the interim. A culture showed Hemophilus influenzae and Staphylococcus aureus (Micrococcus pyogenes var. aureus). The discharge did not respond to topical application of penicillin and sulfonamides. On Feb. 16, pus was expressed from the left lacrimal sac, but none was obtained from the right. On March 1, bilateral probing was performed, and the metallic probe was palpated in the nares. This procedure did not relieve the tearing or the discharge. A roentgenogram after injection of iodized oil revealed that the lacrimal sacs were of normal size and shape. No oil entered the nose. Dacryocystorhinostomy was performed on the right side on March 30 and on the left side on June 21. In both operations anterior and posterior flaps were obtained and sutured together by interrupted surgical gut sutures. The tearing and discharge were completely relieved, without any recurrence. The patient was last examined on March 20, 1952.

CASE 3.—M. A. R., a girl, was born on March 10, 1949, by Caesarean section; her weight at birth was 7 lb. 7 oz. (3,374 gm.). The trial labor was 16 hours. The head was deformed; the entire right side had the appearance of bulging anteriorly, and the left side, of being depressed, but bulging posteriorly. A roentgenogram revealed asymmetry of the bones of the calvaria, with bulging on the right side. A suggested deficiency of the right maxillary bone was reported. On April 18, at the age of 5 weeks, considerable purulent material was expressed from the left lacrimal sac through the lower punctum. In November, 1949, a roentgenogram revealed premature closure of the frontal, parietal, and occipital sutures. The chronic dacryocystitis persisted until she was admitted for definitive treatment. On April 17, 1950, an attempt at probing failed, the probe encountered pronounced bony resistance on reaching the area of the nasolacrimal duct. An injection of iodized oil revealed enlargement of the lacrimal sac on the left, and no contrast medium entered the nose. On April 24, dacryocystorhinostomy was performed on the left side. The lacrimal bone was found to be distorted and bowed in so that posteriorly it was considerably deeper than its anterior part. Good anterior mucosal flaps were procured, but the posterior flap of the nasal mucosa was thin and ragged. This was cut off flush with the bony opening, as was the posterior flap of the lacrimal sac. The anterior flaps were sutured together with interrupted surgical gut. Recovery was uneventful. On May 9, conjunctival instillation of fluorescein appeared in the left nostril in a few seconds. The eye was dry, and no discharge was visible. Operation was carried out on May 25 for the craniostenosis and the deformity of the skull.

COMMENT

These three cases illustrate most of the indications for dacryocystorhinostomy in infants and children. The first case was one of acute bilateral phlegmonous dacryocystitis at birth, followed by the bilateral chronic type and a unilateral lacrimal fistula. It is noteworthy that the fistula closed spontaneously after permanent drainage was established. The second case was one of acquired chronic dacryocystitis of unknown origin, with normal-sized lacrimal sacs. The third case

Fig. 2 (Case 3).—Left chronic dacryocystitis with craniostenosis. Note asymmetry of the face.

Fig. 3.—Injection of the left lacrimal sac with iodized oil U. S. P. Note asymmetry of the calvaria.

was probably one of an anomaly of the bones related anatomically to the lacrimal sac and nasolacrimal duct. Injections of iodized oil U. S. P. revealed a dilated, atonic lacrimal sac in two cases and a sac of normal size and shape in the third. In all cases the obstruction was at the upper end of the nasolacrimal duct. The dilatation of the sac was directed forward and was greater below the internal canthal ligament, as shown by Fox.[12] The roentgenographic outline of a sac filled with iodized oil is a helpful guide in performing the necessary operation.

In all three cases excellent results were obtained with a procedure designed to utilize the mucosal flaps of the nose and lacrimal sac. From the cases reported in the literature, it appears that the greatest percentage of success is found in cases in which flaps are used to cover the edges of the bony opening. This prevents encroachment by bony proliferation and granulation tissue. The anterior flap is the more important of the two; this was pointed out by Corboy,[13] who simplified his procedure by eliminating the posterior flap entirely and making his incision to obtain a large anterior flap. The exposure was not found to be any more difficult than that in an adult. The opening in the lacrimal bone was made more easily in these infants because the bony tissue was thinner and softer. It was comparatively easy to break through the lacrimal bone behind the posterior crest and make a hole large enough to permit the introduction of a Kerrison punch. The size of the opening was made the same as in an adult, i. e., about 1.5 by 1.5 cm. The position of the opening was such as to include part of the anterior lacrimal crest and was carried down to the level of the entrance into the nasolacrimal duct. Only an occasional ethmoid cell was encountered and removed. As a rule, the mucosa of the nasolacrimal duct was curetted. The agar nasi was easily removed to enlarge the opening anteriorly. The use of a fine, fully curved atraumatic® needle, about ¼ in. (6.4 mm.) in diameter, with a straight or curved small mosquito clamp as a needle holder, helped considerably in suturing the flaps. No attempt was made to irrigate after operation. The reaction from this amount of surgical trauma was amazingly small. Primary healing occurred in all cases.

General anesthesia, induced with ether and oxygen, was used in all three cases. An intratracheal catheter helps considerably in maintaining an adequate airway. If bleeding is controlled before the nasal mucosa is opened, very little blood will enter the nasopharynx, for the mucosa does not bleed a great deal. A preliminary nasal pack soaked with epinephrine, as used in adults, would keep any blood from entering the pharynx.

SUMMARY

Dacryocystorhinostomy in infants and children is as successful as in adults. The procedure is no more difficult; in fact, the bony opening is made more easily. Satisfactory flaps can be obtained for uniting nasal mucosa to mucosa of the lacrimal sac. The three cases reported illustrate the common indications for this procedure in children. Fortunately, in all but a few cases of congenital obstruction of the lacrimal duct with dacryocystitis the condition can be treated and cured with conservative management or probing. There is no need to consider extirpation of the sac when dacryocystorhinostomy relieves not only the infection but also the tearing.

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OCULAR INVOLVEMENT IN LYMPHOMATOUS DISEASE

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OCULAR involvement in lymphomatous disease has been a sufficiently uncommon event to warrant isolated and collected case reports at various intervals in the ophthalmologic literature. Until recent years, the ocular manifestations were usually reported as ophthalmologic entities, and little attention was given to the occurrence of systemic disease, either prior to or following ocular involvement.

The opinion commonly expressed in the older ophthalmologic literature is that isolated ocular lymphoma generally is not followed by systemic involvement. This stands in conflict with the more recent concepts that appearance of a lymphoma anywhere in the body heralds eventual lymphomatous dissemination, though it be many years distant.

The problem of whether a simple ocular lymphoma should be considered as the first manifestation of a systemic disease has not been settled. Since the ophthalmologist rarely has the privilege of seeing the patient who suffers systemic involvement without recurrent ophthalmic disease, the question is one which will probably be determined only after many more cases of ocular lymphoma have been followed to their ultimate termination.

This paper presents five new case reports of patients with lymphomatous involvement of the eye seen at the University of Chicago Clinics in the past six years. One of these patients had bilateral blindness as a rare complication of systemic lymphosarcoma. Two others had ocular involvement in the course of systemic disease. Two are apparently without extraocular manifestation of disease one and four years respectively following therapy of the eye.

A survey has been made of many of the previously reported cases of this form of lymphomatous disease. The tables attempt to correlate the time of ocular involvement and the time of onset of the extraocular disease, and from these tables certain limited conclusions can be drawn regarding prognosis and other features. Some of the histologic, therapeutic, and other aspects of the ocular lymphomatous diseases are briefly discussed.

REPORT OF CASES

CASE 1.—*Bilateral blindness eight years after onset of systemic disease.*

J. G., a man aged 31, was first seen at the University of Chicago Clinics in October, 1945. He gave a history of recurrent lymphadenopathy in the preceding 2½ years, which had been

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diagnosed as Hodgkin's disease after biopsy of an inguinal lymph node. He had had two courses of x-ray therapy, which had reduced the swellings in the postural, axillary, and inguinal regions.

When first seen at the clinics, he had small, nontender lymph nodes in the right epitrochlear and left postural and occipital regions. His peripheral blood count was normal and the roentgenogram of the chest showed nothing unusual. He was followed in the outpatient clinics during the next two years, until April, 1947, when hospitalization was necessitated by increasing fatigue, weakness, and pain in the right groin. An inguinal-node biopsy was then done and the diagnosis of lymphosarcoma was made. He received 28 mg. of nitrogen mustard (methyl-*bis* or -*tris*-[2-chloroethyl]-amine) and was discharged as considerably improved.

In the next year, he was again hospitalized three times for pleural effusion or enlarged nodes and on each occasion was given another course of nitrogen mustard.

From August, 1948, until May, 1951, the patient was functionally well, receiving occasional local x-ray therapy for swollen, painful nodes in the right groin.

In May, 1951, he had an upper respiratory infection, with which he noted tearing and a swelling of the upper left eyelid. When the lid was elevated, he was found to have impaired vision in the temporal field of the left eye. Examination showed a normal right visual field, with a defect in the lower part of the left field and some constriction of the left lateral field border. The fundus of the left eye showed primary optic nerve atrophy. In the temporal region behind the outer canthus of this eye, a 2-cm. mass was noted. Shortly thereafter, he received x-ray therapy from his local physician, directed toward the optic chiasm.

Although the external mass subsided, vision in the left eye was completely lost by July, 1951, and the right eye showed nasal hemianopsia. In the temporal fields of the right eye the visual acuity was 6/200, with intact color vision and no extraocular paralyses.

On July 18, 1951, craniotomy showed that the left optic nerve, in its postchiasmal portion, was compressed by a tumor mass, which had narrowed it to the size of a thread. The tumor, which was invading the dura and portions of the cranial bone, was also pressing upon the right optic nerve and appeared to have its main mass below the optic chiasm. It was extremely friable and widespread, and fear of hemorrhage interdicted its removal. The left optic nerve was severed at the area of constrictive destruction to allow release of tension upon the right optic nerve, in the hope of its salvage. A portion of dura containing tumor was excised, and the cranium was closed. Postoperative x-ray therapy to the chiasmal area was given. Microscopic examination of the excised tumor in the dura showed typical lymphosarcoma.

For the first few postoperative days the patient did well, retaining the preoperative temporal vision in the right eye. He then lost all sight in the right eye and became somewhat disoriented. He was discharged home on the 10th postoperative day, with slowly increasing clarity of the sensorium but with complete blindness. The patient is to be followed in the outpatient department.

Involvement of cranial nerves in lymphosarcoma is rare, and a search of the literature discloses no other case in which blindness developed similarly as a complication of the disease.

CASE 2.—*Retro-orbital lymphoblastoma without systemic involvement for four years.*

G. W., a housewife aged 66, was first seen in July, 1947, complaining of swelling of the right orbit, gradually increasing blurring of vision in the right eye for seven months, and diplopia for one month.

Examination showed proptosis of the right eye, with restriction in outward and downward motion of the globe. Exophthalmometric (Hertel) readings were 15.5 mm. for the left eye and 24 mm. for the right eye. A hard, immobile mass, of the consistency of cartilage, could be felt between the right bulb and the lower nasal orbital ridge, extending under the surface of the globe. A biopsy specimen was interpreted as lymphoblastoma (lymphosarcoma or atypical Hodgkin's disease). The patient received 14 x-ray treatments of 200 to 300 r each, distributed to a right temporal and a left nasal portal over a period of 18 days.

By October, 1947, there was pronounced regression of the exophthalmos, but the diplopia continued and the motion of the right eye was limited to about 20 degrees up, in, and out, with no downward motion.

The patient was seen regularly in the outpatient clinics, and on her last visit, in July, 1951, she continued to have some diplopia, troubling her more with near than with far vision. Blood cell counts remained normal, and there was no sign of orbital recurrence or systemic involvement.

This excellent response to x-ray therapy is typical of the effect of radiation upon lymphomatous tumors in the ocular region.

CASE 3.—*Enlarging orbital lymphoma for three years, with no sign of recurrence or systemic involvement one year after x-ray therapy.*

J. G., a man aged 63, came to the Clinics in October, 1947, because of pain in the outer portion of the left eye. The diagnosis of bilateral minimal simple chronic glaucoma was made, and pilocarpine nitrate, 1%, three times a day, was prescribed. During the period of observation, intraocular tension increased in both eyes, and early field defects developed. An Elliot trephination was done on the right side in February, 1948, followed by a similar operation on the left side in May, 1948.

At his initial examination, in October, 1947, moderate proptosis of the left eye was noted. While he was being seen intermittently in the clinic for medical management of his glaucoma, the proptosis gradually increased. By October, 1948, the lid was swollen, with hyperemia of the conjunctiva. By August, 1949, there was increased drooping of the upper lid, with some blurring of vision and the subjective sensation of looking through a steamy haze.

Further consideration of the proptosis was temporarily abandoned when the patient, in August, 1949, had a cardiovascular accident. In February, 1950, examination showed prominent ptosis of the left eye, closed lids, and limited motion of the bulb. The exophthalmometric reading was 25 mm. Roentgenograms showed no orbital lesion.

The mass continued to enlarge, and biopsy was done in July, 1950. The microscopic diagnosis was lymphoma of the orbit, in the region of the superior tarsal muscle. At this time, the swollen and discolored left eye was pushed outward and downward, and its conjunctiva was injected. The patient was still able to count fingers with this eye. General examination showed a blood pressure varying from 170/90 to 210/110, with slightly enlarged heart and a snapping aortic second sound. The peripheral blood cell counts and sternal marrow were normal. Plasma protein was 8.11 mg. per 100 cc. There were no palpable lymph nodes.

Members of the department of roentgenology advised irradiation without enucleation of the orbital mass and gave 2,045 r over a 15-day period. This greatly reduced the proptosis and increased the vision in the left eye.

By December, 1950 (five months after therapy), the proptosis remained slight, although there was residual displacement of the left eye.

In June, 1951, when the patient was last seen, there was no noticeable exophthalmos. His glaucoma was controlled with pilocarpine, and tension (Schiøtz) was 11.5 mm. on the right and 17 mm. on the left. There was no sign of lymphomatous involvement elsewhere.

It may be conjectured that the glaucoma present in this case was secondary to lymphoid obstruction of the intraocular circulation. The patient continues his clinic visits, and later evaluation will be made to assess the results of the regression following irradiation.

CASE 4.—*Conjunctival involvement two to six years after systemic lymphosarcoma.*

J. G., a man aged 66, was first seen in the Clinics in March, 1950, complaining of lumps under the upper left eyelid of a year's duration.

In 1943, he had noted a movable, nontender mass about the size of a large marble in the left submental region. It had caused him no discomfort and spontaneously disappeared after a few months. In 1947, he noted a lump in the right supraclavicular region, and biopsy, done at another hospital, showed lymphosarcoma. The patient received 3,000 r of x-radiation to the right side of the neck and 300 r each to other nodes in the left cervical and right inguinal regions, with striking reduction in the size of the masses.

In 1948 there developed mild photophobia and conjunctival inflammation of both eyes, and in 1949 he first noted lumps under both upper eyelids. Biopsy of material taken from the mass under the right eyelid led to the diagnosis of lymphosarcoma.

When he was first seen in the Clinics, in 1950, the patient was otherwise asymptomatic and had no pain except for some difficulty in closing his eyes. Examination showed the presence of two large, nontender masses extending down from the conjunctivae halfway over each pupil and freely movable over the underlying eye. Under the raised lids were observed two masses attached to the eyes superiorly. A few small, discrete, nontender nodes were palpable in the cervical, axillary, and inguinal regions. Examinations of the blood and bone marrow revealed nothing of significance.

X-radiation (1,124 r) was given locally to the masses beneath each lid, the eye being protected by a lead shield. The irradiation covered eight days, and 10 days after its completion a small residual conjunctival mass, 2 by 4 mm., was seen in the right eye, and a smaller one was observed in the lateral upper portion of the conjunctiva of the left eye. One month later, there was essentially no residual tumor in the eyelids, although a small node was still present in the left axilla.

At the time of this report the patient has continued to be asymptomatic. However, at his last clinic visit, in June, 1951, nodes could be felt in the right inguinal region, and the tip of the spleen was palpable. The presence of mild ankle edema, particularly on the right side, was noted.

The onset of systemic lymphosarcoma in this case can probably be considered as occurring in 1947, with the enlargement of the supraclavicular node, rather than in 1943, with the unexamined, spontaneously resorbed submental mass. Hence, the ocular involvement in 1949 came two years after onset of the systemic condition.

CASE 5.—*Recurrent involvement of the eyes beginning at least two years after manifestation of extraocular disease.*

B. M., a housewife aged 65, was first seen at the Clinics in January, 1951, with a history of recurrent growths in the skin over a 14-year period. In 1937 she had had an asymptomatic subcutaneous swelling on the posterior aspect of the right leg, which gradually disappeared spontaneously. In 1941 she noted gradual onset of hoarseness, which became progressively worse, and in 1943 operation was performed for removal of "nonmalignant lymphoid tissue" from the vocal cords.

After the operation in 1943 a swelling developed in the left lower eyelid; the mass was excised. Local nodular swellings later developed on the medial aspects of the thighs and about the eyes. In 1944 skin nodules developed on the shoulders and hips.

In 1944 and 1946 she received x-ray treatment to the neck for recurrent hoarseness, and from 1944 to 1950 she had seven operations in the orbital region and conjunctivae for excision of recurrent masses.

When she was first seen at the Clinics, in 1951, she had painless masses in both periorbital regions and both conjunctivae. A firm, fixed, slightly irregular mass lay above the left eye, and a similar, smaller one, below the left eye. Smooth, tan conjunctival masses, up to 1 cm. in diameter, were present in the fornices of each eye, with thickened, proptotic upper lids. The extraocular movements were limited in all six cardinal directions. The general examination showed scattered skin nodules, with soft, discrete, small nodes in the axillary and inguinal regions. The liver and spleen were both palpable 4 cm. below the costal margins. Peripheral blood cell counts were normal, and sternal marrow showed a slight increase of lymphocytes and eosinophiles, but no diagnostic characteristics. The plasma protein was increased (8.2 gm. per 100 cc.). The serum coagulated after 20 minutes at 56 C., and the coagulum did not redissolve on cooling. Bence Jones protein was not demonstrable in the urine.

The observed areas of lymphatic enlargement and the long history without rapid progression suggested a diagnosis of benign follicular lymphoma to the consulting hematologist, and the plasma protein and serum coagulation findings were suggestive of plasmacytoma to the pathologist. However, biopsy of a skin nodule on the right thigh showed tissue densely infiltrated with sheets of closely packed uniform cells, looking like large and medium lymphocytes, only a few resembling plasma cells. The microscopic diagnosis was lymphosarcoma.

X-ray therapy was completed on Feb. 20, 1951, the patient having received 1,883 r D_s (tumor dose) over 15 days to the left orbit and 1,758 r D_s over 14 days to the right orbit.

During the next two months, she received 1 mc. of radioactive phosphorus at eight weekly intervals. Under this regimen, many of the skin nodules decreased in size; the spleen was no longer palpable, and there was considerable diminution of axillary and inguinal adenopathy. However, when the patient was last seen, on Aug. 9, 1951, the liver was still 5 to 6 cm. below the costal margin, and a slight infiltration appeared to be returning in the bulbar conjunctiva of the upper outer portion of the left eye.

If the systemic disease in this case is considered to have begun with appearance of the skin nodules in 1937, the ocular involvement did not occur until six years later. The involvement of the eye came two years later if the hoarseness, in 1943, is taken as the initial point. As an interesting side light, one notes the continual recurrence of ocular masses despite seven surgical excisions. It is yet too early to evaluate the effect of x-ray therapy in this case.

CLASSIFICATION OF THE LYMPHOMAS

The lymphomatous tumors are at present generally considered as manifestations of a single disease of lymphoid tissue.[1] Classification into rigid clinical or pathological categories thus becomes difficult, and changing concepts produce changing classifications. Among the more useful classifications are those listed by Gall and Mallory,[2] Custer,[1] and Heath.[3]

Different investigators have used different classifications and have had their results subsequently challenged for this reason. For example, Törnquist [4] pointed out that in many cases the condition reported as lymphoma of the lacrimal sac and conjunctiva may actually have been giant follicular lymphadenopathy, while Rados,[5] in describing his concept of reticulum cell sarcoma, expressed the belief that in previously reported ocular cases the condition has been misdiagnosed and should properly have been given some other pathological label. The difficulty entailed in making a rigid classification becomes more evident when it is realized that true leukemia may be present as the original disease, may occur late in the course of lymphomatous disease, or may never appear.

In making the tabulations, we shall not attempt in this paper to reclassify any of the pathological designations in the references cited, since no single set of pathological criteria is universally recognized. The types of lymphomas to be considered here are those which have fallen into any of the classification schemes noted above, i. e., Hodgkin's disease, lymphoma (lymphocytoma and lymphoblastoma), lymphosarcoma and reticulum cell sarcoma, and giant follicular lymphoma. Ocular involvement in leukemia will not be considered except when the leukemia occurred as a terminal event in the course of lymphomatous disease.

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Ocular Involvement Preceding Onset of Extraocular Disease.—In Table 1 are listed 18 cases [6] of lymphomatous tumors which first appeared in the ocular region and the ultimate malignancy of which cannot be disputed. In two cases death was caused by local invasion of contiguous structures. In the others, there was demonstrable involvement in the classic systemic locations for lymphomatous disease. In the most spectacular case, a conjunctival lymphoma was kept under observation, with several post-therapeutic local recurrences, for 18 years before it produced systemic manifestations.

It would be desirable to establish criteria by which one could predict the likelihood of generalization of an ocular lymphoma. The paucity of cases, unfortunately, forbids any statistically valid deductions. Moreover, the pathological findings, anatomical distribution, age, and sex distribution in these cases provide no distinguishing features.

With respect to chronological prognosis, it is apparent, in 12 of the 18 cases, that if the disease were going to strike at the extraocular areas, it did so within 1½ years after onset of the initial ocular lesion. In four of the other cases the ocular disease was of three or more years' duration before becoming generalized, and in two no precise time relation was recorded.

Ocular Involvement Following Onset of Extraocular Disease.—In the cases tabulated in Table 2,[7] intervals of from two weeks to six years occurred between

6. (*a*) Bedell, A. J., in discussion on Heath.[3] (*b*) Braley, A. E., and Alexander, R. C.: Virus Studies in Lymphomatoid Diseases of the Ocular Adnexa, Am. J. Ophth. **30**:1369, 1947. (*c*) Butler, T. H.: A Case of Sarcoma of the Lacrimal Sac, Arch. Ophth. **43**:16, 1914. (*d*) Coats, G.: Lymphoma and Lymphosarcoma of the Conjunctiva, ibid. **44**:235, 1915. (*e*) Cookson, H. A., and MacRae, A.: Lymphoid Tumor of the Lacrimal Gland, Brit. J. Ophth. **22**:385, 1938. (*f*) Gall and Mallory.[2] (*g*) Heath.[3] (*h*) Kaufman, S. I.: Mikulicz Syndrome: An Early Manifestation of Hodgkin's Disease; Report of a Case, Eye, Ear, Nose & Throat Month. **29**:257, 1950. (*i*) Metivier, V. M.: Lymphosarcoma of the Eyelid, Brit. J. Ophth. **21**:202, 1937. (*j*) Reeves, R. J.: Lymphoblastoma (Hodgkin's Disease) of the Orbit, Am. J. Roentgenol. **17**:642, 1927. (*k*) Rosenthal, N.; Harris, W., and Kean, A.: Clinical and Radiotherapeutic Considerations of Follicular Lymphoblastoma, ibid. **29**:95, 1933. (*l*) Sédan, J.; Astier, A., and Caudière, M.: Lymphoblastome du sac lachrymal généralisé après étape orbitaire, à la totalité de l'appareil lymphatique, Bull. et mém. Soc. franç. opht. **44**:249, 1939; cited by Törnquist.[4] (*m*) Stansbury, F. C.: Lymphosarcoma of the Eyelid, Arch. Ophth. **40**:518, 1948. (*n*) van Walbeek, K.: A Case of Reticulum Cell Sarcoma of the Plica Semilunaris, Acta ophth. **24**:183, 1946. (*o*) Weve, H.: Ein lymphatische tumor van der traansak, Nederl. tijdschr. geneesk. **1**:696, 1928.

7. (*a*) Bateman, O. J.; Squires, G., and Thannhauser, S. J.: Hodgkin's Disease Associated with Schilder's Disease, Ann. Int. Med. **22**:426, 1945. (*b*) Cooper, E. L., and Riker, J. L.: Malignant Lymphoma of the Uveal Tract, Tr. Am. Acad. Ophth. **54**:116, 1950. (*c*) Francia, C.: Cheratite in morbo di Hodgkin, Rass. ital. ottal. **19**:140, 1950; abstracted, Excerpta Med. XII **9**:692, 1950. (*d*) Gross, P., and Votawa, G. J.: Bilateral Symmetrical Exophthalmos Due to Retrobulbar Lymphosarcoma: Report of a Case, Radiology **31**:620, 1938. (*e*) Jensen, J. P.: Conjunctival Lymphoma, Acta ophth. **18**:67, 1940. (*f*) Kamellin, S.: Uveitis Associated with Hodgkin's Disease: Report of a Case, Arch. Ophth. **31**:517, 1944. (*g*) Kravitz, D.: Hodgkin's Disease of the Lid, ibid. **21**:844, 1939. (*h*) Matteucci, P.: Corneal Lesions in Hodgkin's Disease, Am. J. Ophth. **30**:136, 1947. (*i*) MacKechnie, H. N.: One Case of Hodgkin's Disease Treated Over a Period of 6 Years with Recent Ocular Disturbances, S. Clin. North America **7**:761, 1929. (*j*) Meigs, A. V., and de Schweinitz, G. E.: Round-Celled Sarcoma of the Anterior Mediastinum: Extensive Metastasis, Including the Brain, Both Choroid Coats, Oculo-Motor and Optic Nerves, and External Ocular Muscles, Am. J. M. Sc. **108**:193, 1894. (*k*) Ridley, N. C.:

(Footnote continued on next page)

the onset of extraocular lymphomatous disease and subsequent involvement of the eyes. In one of the three new cases which the present paper adds to this collection, a span of eight years occurred between the two events.

The reports of keratitis or keratoconjunctivitis as a complication of Hodgkin's disease have not given pathological demonstration of Hodgkin's cells in the affected areas. Von Bahr [8] and Törnquist [4] have both described cases in which decreased lacrimation, resulting from cellular infiltration of the lacrimal gland, caused keratoconjunctivitis. In one of these cases closure of the lacrimal canaliculi produced

TABLE 1.—*Ocular Involvement Preceding Onset of Extraocular Lymphomatous Disease*

Reference	At Time of Eye Manifestation: Sex	At Time of Eye Manifestation: Age, Yr.	Pathology Location	Time Until Extraocular Involvement	Sequelae
Bedell [6a]	F	52	Lymphoma Pericorneal	18 yr.	Death; no further details
Braley and Alexander [6b]	M	?	Giant follicular lymphoma Behind upper lids	8 yr.	No further details
Butler [6c]	F	17	Lymphosarcoma Lacrimal sac	Local spread leading to death within 3 yr.	
Coats [6d]	F	25	Lymphosarcoma Conjunctiva	10 mo.	No further details
Cookson and MacRae [6e]	F	9	Lymphosarcoma Lacrimal gland	1 mo.	Death
Gall and Mallory [2]	..	?	Lymphosarcoma Lid	?	Death
Heath [3]	M	55	Lymphoma Conjunctiva	6 mo.	No further details
Heath [3]	M	8	Reticulum cell sarcoma Orbit	9 mo.	Death
Heath [3]	F	87	Lymphosarcoma Orbit	Died in 1½ yr.	No further details
Heath [3]	M	34	Lymphoma Conjunctiva	9 mo.	Death
Kaufman [6h]	F	55	Keratitis sicca	6 wk.	Generalized Hodgkin's disease and death
Metivier [6i]	M	11	Lymphosarcoma Eyelid	2 mo.	Patient alive after 2 yr.
Reeves [6j]	F	29	Lymphoma Orbit	8 mo.	Patient alive after 4 yr.
Rosenthal and others [6k]	F	56	Giant follicular lymphoma with exophthalmos	Death 9 yr. later (no further details)	
Sédan and others [6l]	F	?	Lymphoblastoma Lacrimal sac	Death 7 mo. later (no further details)	
Stansbury [6m]	M	49	Reticulum cell sarcoma Lower lid	Death in 40 days; massive systemic involvement	
van Walbeek [6n]	M	58	Reticulum cell sarcoma Plica semilunaris	Local spread, leading to death in 1½ yr.	
Weve [6o]	F	59	Lymphoid tumor Lacrimal sac	Disease reported to have been generalized; no further details	

an excellent response. Therefore, since the pathological changes of Hodgkin's disease have not been demonstrated in the cases of keratitis and keratoconjunctivitis reviewed here, it must be assumed that these lesions are secondary to a lacrimal deficiency following subclinical infiltration with Hodgkin's cells of the more susceptible lacrimal gland, rather than to direct lymphomatous infiltration of the cornea.

An Unusual Complication of Hodgkin's Disease, Tr. Ophth. Soc. U. Kingdom **49**:399, 1929. (*l*) Sachs, B.: Eye Conditions in Leukemia, Arch. Ophth. **57**:474, 1928. (*m*) Törnquist.[4] (*n*) Rosenthal, Harris, and Kean.[6k]

8. von Bahr, G.: A Case of Uveo-Parotitis with Perivasculitis and Other Rare Symptoms, Acta. ophth. **16**:101, 1938.

Ocular and Extraocular Involvement Present on First Examination.—Priority of lesions was conclusively established in the cases listed in Table 3,[9] in which features of both ocular and extraocular lymphomatous disease were observed on first examination. In these cases the patient's ocular condition originally led him to the physician. General examination then revealed the existence of lymphaden-

TABLE 2.—*Ocular Involvement Following Onset of Extraocular Lymphomatous Disease*

Reference	Sex	Age at Onset, Yr.	Extraocular Pathology	Time Prior to Ocular Involvement	Nature or Site of Ocular Lesion	Sequelae
Bateman and others [7a]	M	43	Hodgkin's disease	23 mo.	Blindness; Schilder's disease (?)	Death shortly after
Cooper and Riker [7b]	M	24	Reticulum cell sarcoma	3 yr.	Iridocyclitis	Death in 1½ yr.
Francia [7c]	M	26	Hodgkin's disease	?	Keratoconjunctivitis; no further details	
Gross and Votawa [7d]	F	54	Lymphosarcoma	1 yr.	Periorbital, bilateral	Death in 5 mo.
Jensen [7e]	M	32	Lymphosarcoma (of tonsil)	Several mo.	Conjunctival fornices	No further details
Kamellin [7f]	M	26	Hodgkin's disease	3-4 wk.	Uveitis	No further details
Kravitz [7g]	F	79	Reticulum cell sarcoma	3 yr.	Orbit	Patient alive after 1 yr.
Matteucci [7h]	F	27	Hodgkin's disease	4 yr.	Bilateral keratitis	No further details
MacKechnie [7i]	M	25	Lymphosarcoma	5 yr.	Orbit; lid	No further details
Meigs and de Schweinitz [7j]	M	21	Lymphosarcoma (?)	2 mo.	Choroid; orbit	Death in 10 days
Meigs and de Schweinitz [7j]	M	43	Lymphosarcoma (?)	2 wk.	Orbit	Death in 3-4 days
Ridley [7k]	M	59	Lymphosarcoma	3 yr.	Lacrimal glands	Death in 2 yr.
Sachs [7l]	F	63	Hodgkin's disease	1 yr.	Uveitis	No further details
Sachs [7l]	F	28	Hodgkin's disease	6 yr.	Bilateral keratitis	Patient alive after 3 yr.
Törnquist [4]	M	46	Reticulum cell sarcoma (giant follicular type [?])	2 yr.	Conjunctival fornices	Patient alive after 2 yr.
Rosenthal and others [6k]	F	51	Giant follicular lymphoma	3 yr.	Exophthalmos	Patient alive after 14 yr.
Rosenthal and others [6k]	F	28	Giant follicular lymphoma	4 yr.	Exophthalmos	Death in 3 yr.
Rosenthal and others [6k]	F	32	Giant follicular lymphoma	2 yr.	Exophthalmos	Death in 1 yr.

TABLE 3.—*Ocular and Extraocular Lymphomatous Involvement Noted Together at First Examination*

Reference	Age	Sex	Pathology	Ocular Structure Involved	Patient's Status
Avery and Warren [9a]	50	F	Hodgkin's disease	Cornea (leukomas)	Alive after 4 yr.
Chambers [9b]	64	M	Giant follicular lymphoma	Lids and conjunctiva	Alive after 7 mo.
Rados [5]	29	M	Reticulum cell sarcoma	Conjunctiva	Died in 5 mo.
Reeves [6j]	28	M	Lymphoma (Hodgkin's)	Conjunctiva	No further details
Saradarian [9c]	59	M	Lymphoma	Conjunctiva	Died shortly after
Tooke [9f]	65	M	Lymphosarcoma	Both lids	Alive after 6 mo.

9. (*a*) Avery, J. W., and Warren, J. W.: An Unusual Case of Hodgkin's Disease, Arch. Ophth. **26**:1019, 1941; **34**:318, 1945. (*b*) Chambers, B. M.: Therapy of Giant Follicular Lymphoma with Nitrogen Mustard: Report of a Case, ibid. **43**:520, 1950. (*c*) Rados.[5] (*d*) Reeves.[6j] (*e*) Saradarian, A. V.: Bilateral Subconjunctival Lymphoid Infiltration: Report of a Case, Arch. Ophth. **24**:980, 1940. (*f*) Tooke, F. T.: A Case of Aleukemic Lymphosis Involving the Upper Lids, with Pathologic Findings, Brit. J. Ophth. **23**:444, 1939.

opathy and/or splenomegaly or hepatomegaly, of which the patient had been unaware.

These cases demonstrate that systemic disease may already be present elsewhere at the time of its initial ocular manifestation. The alert ophthalmologist who observes a mass in the ocular region will inquire whether there have ever been masses elsewhere in the body and will palpate the areas of the cervical, occipital, preauricular and postauricular lymph nodes. If it is undesirable to have the patient undress, the examiner may attempt crude palpation of the axillary, epitrochlear, and supraclavicular areas through the overlying clothing. These procedures may give immediate clinical evidence of the presence of systemic disease.

Recognition of the presence of the extraocular disease is of vital importance, since newer methods of cytotoxic therapy (nitrogen mustard, radioactive phosphorus) have produced occasional remissions of both the ocular and the extraocular disease. If this systemic therapy gives successful results with the ophthalmic lesion, it can obviate the risk of recurrence following surgical excision and the risk of cataract formation following x-ray therapy to the ocular region.

COMMENT

Susceptible Anatomical Sites.—Numerous tabulations [10] have been made of the most frequent locations of ocular lymphomas. Secondary lesions have been found anywhere in the eye and its adnexa, although the greatest predilection is exhibited for those sites in which original growths are more restricted, namely, the conjunctiva, lacrimal glands, lids, and orbit. This predilection reflects the histological evidence that lymphoid tissue is normally found in these regions, and it suggested to Coats [6d] that the tumors arise from preexisting cells as a "local expression of a general overactivity of the lymphopoietic apparatus." Other theories hold that ocular lymphomatous disease can arise from diapedesis of lymphocytes through the blood or can originate in fetal remains the presence of which are not noted in ordinary histological studies. This disagreement regarding the etiology and mechanism of ocular involvement in lymphomatous disease indicates that the solution to the problem awaits clarification of the general disease process.

Incidence.—A survey of previously listed figures for the incidence of this condition shows that systemic lymphomas were responsible for about 6% of all deaths [11] in a large urban area, and that the eyes are apparently involved [12] in 1 to 2% of cases of lymphomatous disease. In a small series of cases of giant follicular lymphoma [6k] exophthalmos was noted in 40%. Lymphomas have been found to comprise anywhere from 2 to 10% of all orbital tumors [13] and were noted in 0.2% of a collection of 11,500 eyes in an Army pathological collection.[14]

10. (*a*) Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc., 1951. (*b*) Heath.[3] (*c*) McGavic, J. S.: Lymphomatoid Disease Involving the Eye and Its Adnexa, Arch. Ophth. **30**:179, 1943.

11. Craver, L. F.: Lymphomas and Leukemias, Bull. New York Acad. Med. **23**:79, 1947.

12. (*a*) Heath.[3] (*b*) Reeves.[6j] (*c*) Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: A Study of 196 Cases with Biopsy, J. A. M. A. **115**:17 and 112, 1940.

13. (*a*) Benedict, W. L., and Martens, T. G.: Malignant Lymphocytic Tumors of the Orbit, S. Clin. North America **26**:871, 1946. (*b*) Forrest, A. W.: Intraorbital Tumors, Arch. Ophth. **41**:198, 1949. (*c*) Heath.[3] (*d*) Iles, A. E., and Short, A. R.: Orbital Tumours, Brit. J. Surg. **31**:147, 1943. (*e*) Ingalls, R. G.: Orbital Tumors, Am. J. Ophth. **32**:1595, 1949.

14. Rones, B., cited by Heath.[3]

15. Footnote deleted.

Therapy.—An awareness of the lesion will lead to biopsy and diagnosis. Present-day belief is that x-ray therapy is the method of choice. Reese [10a] has discussed the use of this technique, and he believes that surgery is indicated only so far as it is necessary to establish the diagnosis. All the lymphomas are radiosensitive, and regression usually follows x-ray therapy. Lochman [14] pointed out the roentgenologist's therapeutic dilemma: A large dose of radiation may destroy the tumor but provoke later cataract formation, whereas with a smaller dose the danger of cataract may be diminished but risk of recurrence of the tumor increased.

The recently available cytotoxic agents are probably best reserved for those cases in which disseminated disease has concomitantly been observed.

Prognosis.—Data accumulated by Catlin,[16] Stout,[17] and Craver [11] indicate that lymphosarcoma of the head and neck has a prognosis twice as good as when the lesions occur elsewhere. Block and Jacobson [18] stated that three types of lymphomatous conditions have, in their experience, been known to pursue long courses without dissemination. Their areas of location are the orbit, nasopharynx, and stomach.

However, "The clinical course is relentless," Heath [3] stated regarding ocular lymphomas, "and patients ultimately wind up with the general disease." He cited at least six cases of conjunctival lymphoma which was generalized. McGavic [10c] noted the appearance of extraocular disease in 6 of 17 cases of primary ocular lymphosarcoma. Benedict and Martens,[13a] in examining 19 patients with orbital lymphosarcoma, found that at least 4 had died as a result of tumor dissemination.

Heath further noted that patients with ocular involvement as part of a generalized lymphoma have an average outside prognosis of two years. The follow-up data in Tables 2 and 3, when such data have been available, are essentially in agreement with this figure.

SUMMARY

Five new cases of involvement of the eyes in the lymphomas are presented. In one of these cases the extremely rare complication of bilateral blindness occurred in the course of systemic lymphosarcoma.

A survey of the time relationship between ocular involvement and the onset of extraocular lymphomatous disease is made. It would indicate that isolated lymphoma of the eye or its adnexa must be regarded as a potentially generalized lesion, even though systemic spread may not occur for many years. These data augment the evidence supporting more recent concepts of the subject.

Roentgen-ray therapy is advocated as the present treatment of choice for localized ocular lesions.

Drs. James Crosbie, David Lochman, Matthew Block, Leon Jacobson, and William Bethard, of the University of Chicago Clinics, furnished information on the new cases of ocular lymphoma which have been presented in this report.

16. Catlin, D.: Lymphosarcoma of the Head and Neck, Am. J. Roentgenol. **59**:354, 1948.
17. Stout, A. P.: Results of Treatment of Lymphosarcoma, New York J. Med. **47**:158, 1947.
18. Block, M., and Jacobson, L. O.: Management of the Lymphomas, M. Clin. North America **35**:102, 1951.

PATHOGENESIS OF INTRAOCULAR HYPERTENSION IN CASES OF ARTERIOVENOUS ANEURYSM

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AND
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INTRAOCULAR hypertension is a fairly constant symptom in patients with aneurysm of the cavernous sinus and the internal carotid artery. We have found it in each of five patients recently examined. Three times it was unilateral and affected only the eye on the same side as the lesion; twice it was bilateral.

The present work is the report of a new case of arteriovenous aneurysm complicated by intraocular hypertension. The use of recent techniques—measurement of the episcleral venous pressure, measurement of the resistance to the aqueous flow, and calculation of the volume of this flow—has thrown some light on the mechanism of intraocular hypertension.

REPORT OF A CASE

M. J., aged 17 years, was wounded in June, 1950, in a road accident. He sustained a fracture of the skull, with depression of the right frontotemporal region. His condition steadily improved in the weeks following the accident. Recovery seemed complete, but at the end of 1951 a swelling appeared in the superior inner angle of the right orbit. It increased progressively and was complicated by exophthalmos.

Ocular Examination (Nov. 29, 1951).—Examination showed a large swelling on the inner border of the right orbit (Fig. 1). A thrill could be felt, and a continuous murmur could be heard, becoming stronger during systole. The veins of the right upper lid were dilated. The exophthalmos of the right eye measured 9 mm.; it was axial, reducible, and pulsatile. The veins of the palpebral and bulbar conjunctiva were dilated (Fig. 2). No aqueous veins were visible. The iridocorneal angle was normal. The dilated right pupil reacted poorly to direct light stimulation and during convergence, but responded well to consensual stimulation. The optic disk was pale. The retinal veins were larger in the right eye than in the left. The central artery of the retina was under normal tension in each eye. Intraocular tension was 8 mm. Hg higher in the right eye than in the left eye (right eye, 28 mm. Hg; left eye, 20 mm. Hg).

Vision in the right eye was reduced to 2/10, with narrowing of the temporal field (Fig. 3).

Cerebral Arteriography.—An arteriovenous aneurysm between the internal carotid artery and the cavernous sinus caused a prominent dilatation of the ophthalmic vein. The blood entering the internal carotid artery passed directly into the venous system at the level of the aneurysm, never reaching the cerebral arteries above the lesion (Fig. 4).

STUDY OF THE MECHANISM OF INTRAOCULAR HYPERTENSION

According to the hypothesis that the flow of the aqueous humor (F), the resistance to the aqueous flow (R), and the venous pressure where the aqueous

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veins join the conjunctival and episcleral vessels (Pv) are the main factors in ocular pressure (Poc), as expressed in the formula

$$Poc = (F \times R) + Pv .$$

intraocular hypertension can result from (a) increased aqueous flow, (b) increased resistance to the flow, or (c) increased conjunctival and episcleral pressure.

In the case reported in this paper, we measured the venous pressure and the resistance to the aqueous flow, and from these values we calculated the intraocular flow.

A. Measurement of Venous Pressure.—Measurement of the venous pressure was made by a small transparent chamber attached to a water manometer, similar to that used by Thomassen.[1] We determined, with the slit lamp, the minimum pressure which collapsed the conjunctival vessels, visibly dilated in Figure 2.[2]

Fig. 1.—Swelling on the inner border of the right orbit due to dilatation of the ophthalmic vein.

B. Measurement of Resistance to Aqueous Flow.—Measurement of resistance to the flow was made with the electronic tonometer and the tonometric tables of Friedenwald, published by Moses and Bruno[3] and Grant.[4] Our method is the same as the one used by Grant.[4]

Normally the ocular tension varies but slightly. This observation signifies that the volume of fluid which penetrates the eye in a given time is equal to the volume of fluid which flows out during the same time. The placing of a tonometer on the

1. Thomassen, T. L.: Acta ophth. **27**:1, 1947.

2. Generally we use for measuring the episcleral venous pressure the manometric apparatus made from a mouse bladder, as described by Goldmann. We prefer this instrument to the transparent manometer used in this case. But the measurement of the venous pressure by using the mouse bladder is possible only if a laminar vein is detected with the slit lamp or if red blood corpuscles are visible in one of the vessels. One then finds the minimum pressure which produces the aqueous inflow, the blood inflow, or the arrest of the flow of red blood corpuscles. The absence of laminar vessel and strong conjunctival hyperemia forced us in the present case to use the transparent manometer.

3. Moses, R. A., and Bruno, M.: Am. J. Ophth. **33**:389, 1950.

4. Grant, W. M.: Arch. Ophth. **44**:204, 1950; **46**:113, 1951.

cornea changes this equilibrium, the foot of the tonometer raising the intraocular pressure and distending the sclerotic.

If the tonometer is kept in place for a prolonged period, the escape of fluid becomes greater than its formation, and the intraocular pressure falls progressively. Several observations by Grant [4] and studies by one of us (R. W.) in collaboration with Prijot [5] have shown that the decrease in tension is due mainly to a reduction in the volume of the aqueous humor.

According to Goldmann,[6] the flow of the aqueous humor from the anterior segment of the eye obeys relatively simple physical laws. Poiseuille's law may be applied: $F = \frac{Pf}{R}$

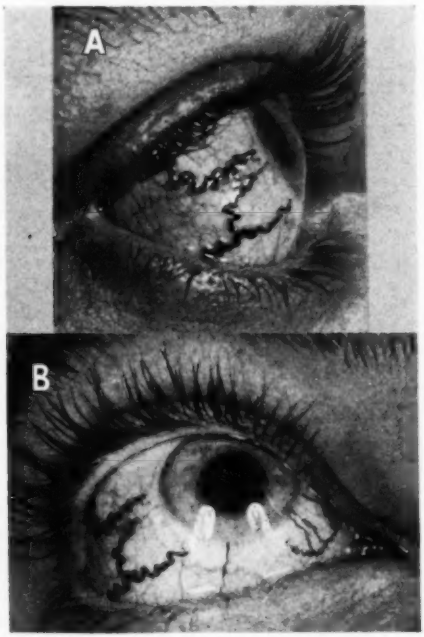

Fig. 2.—Exophthalmos and dilatation of the veins of the bulbar conjunctiva.

where F is the flow of aqueous humor, expressed in cubic millimeters per minute; Pf is the outflow pressure of the aqueous humor, that is, the intraocular pressure (Poc) minus the venous pressure at the point where the aqueous joins the blood (Pv), and R is the resistance offered to the passage of aqueous humor from the anterior chamber to the point where Pv is measured.

From this formula, we infer that $R = \frac{Pf}{F}$.

5. Weekers, R., and Prijot, E.: Ophthalmologica **123**:1 and 114, 1952.
6. Goldmann, H.: Docum. ophth. **5-6**:278, 1951.

When the tonometer is placed on the globe, the intraocular pressure and the rate of flow of the aqueous are increased. In other experiments we have shown that, on the contrary, the resistance remains constant (Weekers and Prijot [5]).

Friedenwald's tables published by Moses and Bruno [3] make possible the calculation of the increase of *Poc* during the compression test. Tonometric pressure (*Pt*) is the pressure of the globe when the tonometer is placed on the cornea. Pt_1 is the tonometric pressure at the beginning of the test, and Pt_2, the tonometric pressure at the end of the test, i. e., after five minutes. The average tonometric

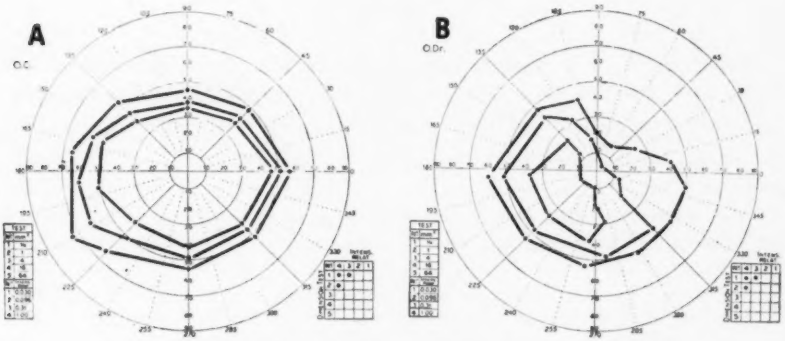

Fig. 3.—Reduced visual field caused by compression of the optic nerve.

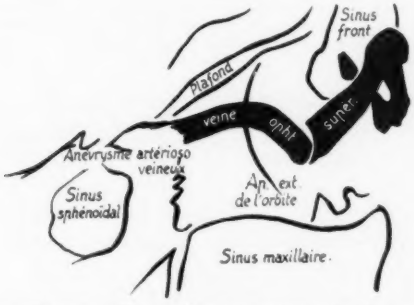

Fig. 4.—Cerebral arteriogram. The tracing represents only the part of the arteriogram corresponding to the aneurysm and to the orbital region. The ophthalmic vein is considerably enlarged.

pressure during the course of the test is calculated accurately enough by the arithmetic mean: $\frac{Pt_1 + Pt_2}{2}$.

The average increase in pressure during the test is calculated from the formula $\frac{Pt_1 + Pt_2}{2} - Poc$.

On the other hand, Friedenwald's tables published by Grant [4] show the increase in flow of the aqueous humor during the compression test. V_1 is the reduction in volume of the globe at the beginning of the test, and V_2 the reduction in volume at the end of the test. Friedenwald's tables take into account the indentation of the cornea and the retraction of the sclera.

The volume of liquid expressed from the globe during the five minutes of the test is $V_2 - V_1$. The quantity of liquid expressed per minute is $\frac{V_2 - V_1}{5}$.

During the compression test $R = \frac{Pf + \left(\frac{Pt_1 + Pt_2}{2} - Poc\right)}{F + \left(\frac{V_2 - V_1}{5}\right)}$.

Since R is not modified during the test, and since Poiseuille's law postulates that $R = \frac{Pf}{F}$

$$R = \frac{\frac{Pt_1 + Pt_2}{2} - Poc}{\frac{V_2 - V_1}{5}}.$$

Consequently, the compression test performed with the electronic tonometer allows direct measurement of the resistance to the aqueous flow outside the globe.

C. Calculation of Rate of Aqueous Flow.—According to Poiseuille's law, $F = \frac{Pf}{R}$ the ocular pressure minus the episcleral venous pressure gives the outflow pressure: $Pf = Poc - Pv$.

The compression test with the electronic tonometer, on the other hand, gives the value of the resistance, thus allowing the calculation of the rate of flow.

Average Values for Five Measurements Made During One Week's Hospitalization

	R. E.	L. E.
Ocular pressure (mm. Hg)	26.7	18.5
Episcleral venous pressure (mm. Hg)	20.0	12.0
Outflow pressure (mm. Hg)	6.7	6.5
Resistance to flow	5.6	6.7
Rate of flow (cu. mm./min.)	1.1	1.0

Goldmann's fluorometer allows direct measurement of the aqueous flow. The value of the flow calculated by the compression method and the value measured by Goldmann's method are approximately the same (Goldmann [6]; Grant [4]; Weekers and Prijot [5]).

In applying these methods to the present case, we have obtained the average values shown in the Table (average of five measurements made during one week's hospitalization).

COMMENT

From our experiment, ocular hypertension in cases of aneurysm of the internal carotid artery and cavernous sinus results essentially from the increased blood pressure in the episcleral and conjunctival veins. In this particular case, the pressure in these veins was increased by 8 mm. Hg (right eye, 20 mm. Hg; left eye, 12 mm. Hg), and the ocular pressure was increased by 8.2 mm. Hg (right eye, 26.7 mm. Hg; left eye, 18.5 mm. Hg). The resistance offered to the flow of the aqueous humor was not increased (right eye, 5.6 and left eye, 6.7). Consequently, the calculation of the flow of the aqueous humor shows no alteration on the side of the lesion (right eye, 1.1 cu. mm. per minute, and left eye, 1.0 cu. mm. per minute).

SUMMARY

Measurements of (*a*) the resistance to the aqueous flow, (*b*) the rate of aqueous flow, and (*c*) the episcleral venous pressure in a case of aneurysm of the internal carotid artery and cavernous sinus with unilateral intraocular hypertension show that the intraocular hypertension was due to increased episcleral venous pressure.

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Clinical Notes, New Instruments and Techniques

A METHOD OF PREVENTING RETAINING SUTURES FROM CUTTING INTO GRAFTS

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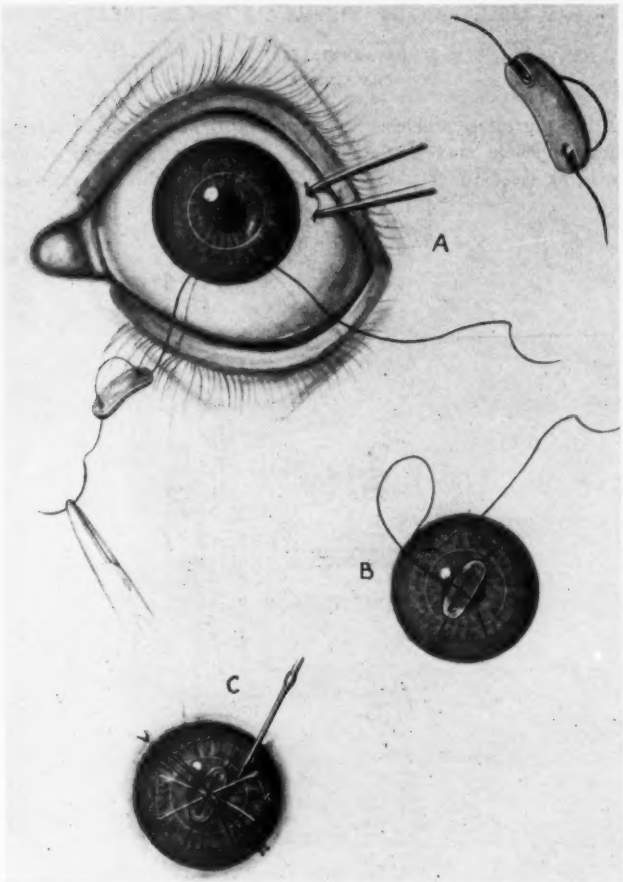
VARIOUS types of plastic caps, or contact lenses, have been employed for maintaining contact between the corneal graft and the recipient cornea in an attempt to avoid injury to the graft from direct sutures or from the pressure of overlying sutures. The first of these, reported by Fritz,[1] was a standard fitted contact lens which exactly covered the cornea. Sutures were passed through perforations at intervals along the edge of the lens and attached to the corneoscleral limbus. In this way, no sutures were in contact with the graft. This method proved unsatisfactory because the absence of air and lacrimal fluid in the wound area delayed healing.

A later model by Worcester [2] had a clover-leaf-like shape and allowed free circulation of air and lacrimal fluid. This method of holding the graft in place was found satisfactory, the only objection being that each cap had to be molded to the curvature of the patient's eye, a procedure which is especially difficult in cases of conical cornea.

The plastic cap illustrated (Figure, *A*) covers only a portion of the transplant itself and protects the central area, where sutures cross and pressure is the greatest (Figure, *C*). Since the incision line is entirely exposed, healing takes place undisturbed. The cap has a second advantage in facilitating removal of sutures. A needle knife (Figure, *C*) or the blade of a pair of scissors may easily be slipped beneath the slightly elevated sutures without the risk of damage to the cornea, such as is ordinarily encountered.

1. Fritz, A.: Am. J. Ophth. **33**:1236, 1950.
2. Worcester, J. T.: Am. J. Ophth. **35**:357, 1952.

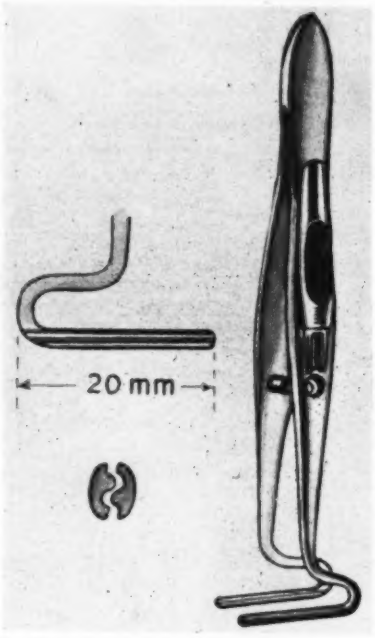


Plastic caps to protect the corneal graft from injury by sutures.

PTOSIS CLAMP FOR HOLDING THE LEVATOR MUSCLE DURING RESECTION OF THE LEVATOR PALPEBRAE

RAYMOND BERKE, M.D.
HACKENSACK, N. J.

ONE OF the greatest problems in performing the operation of resection of the levator palpebrae has been the difficulty of holding the levator tendon securely while it is being freed from its several attachments. If three traction sutures are



The ptosis clamp.

inserted into this tendon, as advocated by Blaskovicz, the sutures always get twisted, cause bunching of the levator muscle, and tend to pull out.

To meet this need, a ptosis clamp has been devised which we at the Ophthalmological Institute have used for the past two years and have found very satisfactory for grasping and holding the levator tendon securely.

This clamp is much like an ordinary extraocular-muscle clamp except that the biting arms of this new instrument are 20 mm., rather than 10 mm., long (Figure).

Corrugations to prevent slipping have been placed inside the biting arms of this ptosis clamp. A sliding attachment locks the blades securely together and requires only one hand to manipulate. Teeth or pins on the biting blades have been tried on other models but have been discarded because of the difficulty in sliding such clamps under the levator muscle and because of the difficulty in cleaning.

This instrument may be procured from the following instrument makers: E. B. Meyrowitz Surgical Instruments Co., Inc.; V. Mueller and Company, and Storz Instrument Company.

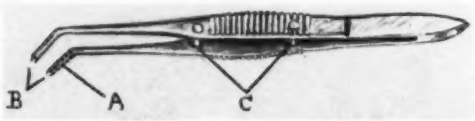
SPECIAL SUTURING AND FIXATION FORCEPS

CONRAD BERENS, M.D.
NEW YORK

THE SPECIAL forceps [1] described here has been found to be especially valuable in cataract extraction, in corneal transplantations, and in grasping fine needles for muscle operations and for plastic surgery of the eyelids.

The suturing forceps is fairly delicate but provides a firm grip because of two fine teeth on each blade (Figure).

The rough serrations (*A*) aid in grasping sutures and needles, particularly special [2] blue nylon sutures with a ⅜-circle, cutting-point atraumatic® needle used



Special suturing from fixation forceps.
A, rough serrations used in grasping sutures and needles; *B*, fine teeth (160-degree angle to blades) useful in grasping the lips of corneal and scleral wounds and the tips of fine needles, as well as in fixation; *C*, two extensions which prevent blades from overriding.

in plastic surgery of the eyelids and in muscle surgery. When the medial and lateral rectus muscles are operated upon, white nylon sutures are employed.

The two fine teeth on each blade (*B*) are most useful in corneal suturing and for scleral fixation in cataract extractions. The teeth are directed at an angle of approximately 160 degrees to the blades, facilitating grasping of the lips of the corneal and scleral wounds. The wide aperture between the teeth on one side permits the tips of fine needles to be grasped. The two extensions between the shafts (*C*) prevent the blades of the forceps from overriding.

708 Park Ave.

This study was aided by a grant from the Ophthalmological Foundation, Inc.

1. Made by Storz Instrument Company, St. Louis.
2. Made by Davis & Geck, Inc., Brooklyn (D & G No. P. 417).

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

COEXISTENCE OF INTRAOCULAR MELANOMA AND LYMPHATIC LEUKEMIA

IN A REVIEW of the literature, we have been unable to find a single case of the coexistence of intraocular melanoma and lymphatic leukemia.[1] It is therefore quite probable that the case to be reported is the first recorded instance of this unusual concomitance.

Peripheral Blood Studies in a Case of Lymphatic Leukemia and Intraocular Melanoma

Date	White Blood Cells	Neutrophiles	Lymphocytes	Monocytes	Eosinophiles	Basophiles	Band Forms	Hemoglobin, Gm./100 Cc.	Comment
10/ 9/51	16,750	30	66	3	1	..	..	13.5	Mature lymphocytes; poikilocytosis
10/26/51	28,600	54	34	5	1	1	5	14.0	.....
10/29/51	Total protein, 7.54 gm./100 cc.; albumin, 4.68 gm./100 cc.; globulin, 2.86 gm./100 cc.; inorganic P, 3.8 mg./100 cc.								
11/ 1/51	Sternal marrow puncture								
11/ 2/51	35,700	28	68	2	2	..	..	13.0	Many immature lymphocytes; several young lymphocytes
11/13/51	32,000	25	73	2	..	..	..	.....	.....
11/20/51	Enucleation of right eye								
11/27/51	28,000	37	59	3	..	..	1	14.5	.....
12/21/51	49,000	40	53	3	2	1	1	13.0	.....

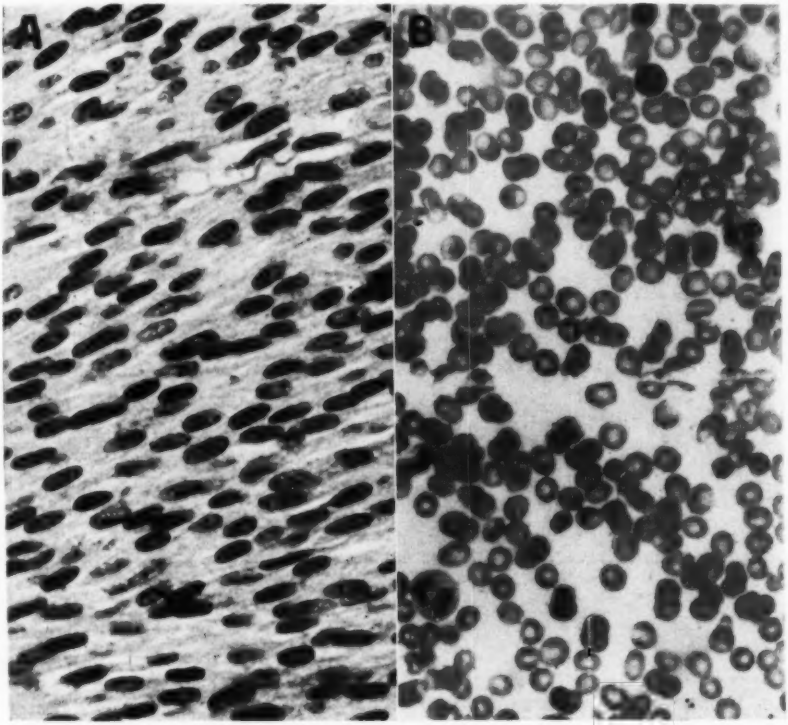
C. L. A., aged 52, a white male veteran, was admitted to the United States Naval Hospital, Philadelphia, on Oct. 9, 1951, with the chief complaint of reduced visual acuity in the right eye. Since June, 1951, the patient had experienced intermittent and momentary flashes of light and colored rings in this eye. The reduction of visual acuity in the right eye was first noted, however, about two weeks prior to his admission to the hospital. The past and family histories were essentially without significance. The systemic review was noncontributory.

Physical examination revealed a normally developed, well-nourished white man, 188 lb. (85.3 Kg.) in weight and 5 ft. 7 in. (170 cm.) in height. He was cooperative, intelligent, and in no apparent distress. The pulse, temperature, respiration, and blood pressure were normal. Except for several tiny pigmented nevi on the back, the results of the general physical examination were not remarkable.

This article has been released for publication by the Division of Publications of the Bureau of Medicine & Surgery of the United States Navy: The opinions and views set forth are those of the authors and are not to be construed as reflecting the policies of the Navy Department.

1. Personal communications with Dr. F. H. Verhoeff, Dr. A. B. Reese, Mrs. H. D. Wilder, Dr. C. D. Theobald, Dr. G. L. Walker, and Dr. T. E. Sanders reveal that none of these correspondents has seen a case of, or read of, such a coexistence.

The principal ocular findings were as follows: Vision in the right eye was limited to perception of hand movements at 1 meter, with fair light perception but with poor and uncertain light projection, not improved with lenses or pinhole disk. There was an extensive separation of the nasal retinal hemisphere, elevated about 3 D. and extending temporalward sufficiently to hide the optic disk and the macula from view. No holes were found. Transillumination was impaired, but not sufficiently that one could be certain that the separation was solid. The intraocular pressure, as determined by digital palpation, was normal. Vision was 20/30 in the left eye, improved to 20/20 with lenses. This eye was normal.



A, photomicrograph of the intraocular malignant melanoma. *B*, photomicrograph of the sternal-marrow film, showing polymorphonuclear leukocytes and cells of the lymphoid series. Courtesy of the Department of Ophthalmology, Hospital of the University of Pennsylvania.

The Kahn reaction of the blood was negative. The findings on routine urinalyses were within normal limits; tests for Bence Jones protein and for melanin gave negative results. The peripheral blood studies are presented in the accompanying table. Genitourinary consultation and intravenous urography failed to reveal any abnormalities. Roentgenograms of the chest, long bones, and pelvis showed no pathological change. However, x-ray photographs of the skull revealed changes reported as "fibrous dysplasia of bone involving the maxilla, zygoma, and frontal bone on the right." In the report it was suggested that syphilitic osteitis and a chronic, low-grade nonsuppurative osteomyelitis" were to be considered in the differential diagnosis. The dental department found and treated a periodontal abscess involving a right upper molar tooth. Examination of the ears, nose, and throat revealed an essentially normal

condition. The medical report stated: "The physical condition is entirely normal except, of course, for the retinal separation and the numerous pigmented moles. There are no abnormal lymph nodes or nodules. The liver, spleen, and kidneys are not palpable."

On Nov. 1, 1951, a sternal bone marrow puncture was done, and the diagnosis of "slight hyperplasia and benign lymphocytosis" was reported.

On ophthalmological consultation it was recommended that enucleation of the right eye be done, for the following reasons: (1) The right eye was useless, with a solid detachment; (2) the right eye probably harbored a melanoma; (3) there was no conclusive evidence of metastasis, and (4) the diagnosis of lymphatic leukemia was not established.

On Nov. 20, the right eye was enucleated by the Frost-Lang technique, and a glass-ball implant was inserted. Postoperative convalescence was uneventful.

The globe was sectioned at Wills Hospital, and the pathological diagnosis, made by Dr. J. McGavic, was spindle cell malignant melanoma of the choroid, Subtype B (Fig. *A*).

In view of the interesting blood picture, the sternal marrow slide was presented to Dr. R. Philip Custer, of Presbyterian Hospital, and subsequently to Dr. L. M. Tocantins, of Jefferson Medical College, for interpretation. Each pathologist, without having previously been informed as to the clinical data in the case, made the diagnosis of chronic lymphatic leukemia (Fig. *B*).

On Nov. 27, repeat peripheral blood films were taken (Table). By Nov. 28 palpable axillary lymph nodes and a palpable spleen were demonstrable.

The patient was the sole support of his ailing mother, who needed her son at home. Therefore, on Dec. 3, he was discharged from the hospital, at his own request.

On Dec. 21 he was seen in the eye clinic of the Naval Hospital. The orbital wound was healing well. A peripheral blood film was taken (Table).

Although the patient promised to return to the hospital for further study "right after Christmas," he has not been seen since Dec. 21. Efforts through the Veterans Liaison, as well as the Red Cross, are being continued in an effort to reexamine him.

Dr. G. D. Theobald, Chicago, and Mrs. H. C. Wilder, Washington, D. C., have reviewed the section of the globe and the sternal marrow film. They concur in the diagnosis of malignant melanoma and chronic lymphatic leukemia.

Lieutenant Commander Rudolph P. Nadbath (MC), U.S.N.
Captain H. G. Bullwinkel (MC), U.S.N.
United States Naval Hospital, Philadelphia 45

Ophthalmological Reviews

USE OF TYPHOID VACCINE IN CONTINUOUS INTRAVENOUS INFUSION IN TREATMENT OF EYE DISEASES

ROBERTO BUXEDA, M.D.
SAN JUAN, PUERTO RICO

ALTHOUGH the use of typhoid vaccine intravenously in the form of a fairly rapid injection has long been a controversial procedure, it has been a most widely used therapeutic agent in ophthalmology. The use of typhoid vaccine intravenously in a slow continuous infusion is a much more recent procedure. In addition to a review of the literature pertaining to the mechanism of the therapeutic action of typhoid vaccine, this paper describes a method of giving typhoid vaccine intravenously as an infusion and presents case reports to demonstrate the advantages of this method.

Since typhoid vaccine was first used, several investigators, particularly in the United States, have attempted to work out procedures of administration whereby rapid and maximal benefit could be obtained without endangering the patient. Much of this work has been done outside the field of ophthalmology. Typhoid vaccine has been used intravenously in the treatment of systemic diseases for nearly 40 years. It has been used extensively during approximately the last three decades in the treatment of innumerable diseases of the eye. Certain ocular conditions, especially those having an inflammatory or a vascular basis, have responded more favorably to this form of therapy. In this respect the nonspecific diseases of the uveal tract, especially the anterior portion, have appeared to be most favorably affected by intravenous injection of typhoid vaccine.

Until 1942 killed typhoid organisms had been administered intravenously in the form of a rapid injection exclusively. The initial injection with this method is between 5,000,000 and 15,000,000 killed typhoid organisms. Subsequent injections, according to various authors, are calculated by increasing by one and one-half times or by doubling the previous injection. These injections are administered on alternate days if no secondary rise in temperature occurs on the day following the injection. If a secondary rise occurs the day after the injection, the subsequent injection is withheld until the temperature becomes normal. From 6 to 10 of these treatments are ordinarily given.

In 1942 Solomon and Somkin [1] used for the first time a suspension of killed typhoid organisms in saline solution in the form of a continuous intravenous infusion for the treatment of subacute bacterial endocarditis.

From the Eye Section, Veterans Administration Hospital, Richmond, Va.

Thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, in partial fulfilment of the requirements for the degree of Master of Medical Science (M. Sc. [Med.]) for graduate work in ophthalmology.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Solomon, H. A., and Somkin, E.: An Improved Method of Obtaining Sustained Controlled Hyperpyrexia with Triple Typhoid Vaccine, Am. J. M. Sc. **203**:736, 1942.

Curry and Shaw [2] were the first ophthalmologists to use a suspension of typhoid vaccine in isotonic saline solution in the form of a continuous intravenous infusion for the treatment of ocular diseases. They, like Solomon and Somkin,[1] employed the method to produce hyperpyrexia. Their method required control of the infusion rate in an effort to maintain a steady elevation of temperature.

The method for presentation differs from Curry and Shaw's [2] in that a much larger number of organisms is administered and the infusion is given at a steady rate. My colleagues and I have not found it necessary to produce a high temperature, and we do not attempt to obtain a certain high degree of temperature by varying the rate of flow.

HISTORICAL DEVELOPMENT OF THE METHOD

In 1925 Allen,[3] in one of the earliest papers on the intravenous use of typhoid vaccine in ophthalmology, stated that numerous workers have found that elevation of the body temperature produced artificially had a favorable influence on an established infection. He stated that animals which had been heated for experimental purposes, by artificial means, had shown a definite resistance to injections of small quantities of bacteria.

In 1913 Torres [4] first used killed typhoid organisms intravenously in South America in the treatment of typhoid. In his report, he described in detail the reactions which occurred with intravenous typhoid therapy and reported successful results. Next, Dessy, Grapiolo, and Fossati [5] compared their results with this new method of using typhoid vaccine with the older one of subcutaneous administration. They concluded that the new method was far superior to the old in the treatment of typhoid. Cecil,[6] reporting on the work of Kraus and Mazza in 1914, stated that these authors had observed that the mortality rate in typhoid was decreased considerably by the intravenous administration of the vaccine.

Typhoid vaccine was probably first used intravenously in the United States for the treatment of disease in 1916 by Miller and Lusk.[7] This vaccine is still the protein material oftenest used for nonspecific protein therapy.

Allen [3] appears to be one of the first authors to have written extensively on the use of killed typhoid organisms intravenously in the treatment of diseases of the eye. At first he used an initial dose of 100,000,000 killed typhoid bacteria. He later modified his technique by giving 30,000,000 organisms, followed by a second dose of 75,000,000 organisms.

In 1931 Nelson [8] suggested that typhoid vaccine be given in coupled or doubled doses, the first dose to be given at any selected time and of a size calculated to produce slight fever, and the second to be given during the height of the fever

2. Curry, J. J., and Shaw, E. A.: Continuous Intravenous Injection of Typhoid Vaccine in Treatment of Certain Ophthalmic Diseases, Arch. Ophth. **42**:123, 1949.

3. Allen, T. D.: Typhoid Vaccine in Ophthalmology, Tr. Sect. Ophth., A. M. A. 1925, p. 135.

4. Torres, F. R.: Vacunoterapia o antigenoterapia antitifica, Semana méd. **22**:1357, 1913.

5. Dessy, S.; Grapiolo, F. L., and Fossati, V.: Nueva vacuna contra la fiebre tifoidea: Notas experimentales y clinicas, Semana méd. **21**:357, 1914.

6. Cecil, R. L.: Nonspecific Protein Therapy, J. A. M. A. **105**:1846, 1935.

7. Miller, J. L., and Lusk, F. B.: Treatment of Arthritis by the Intravenous Injection of Foreign Protein, J. A. M. A. **66**:1756, 1916.

8. Nelson, M. O.: Improved Method of Protein Fever Treatment in Neurosyphilis, Am. J. Syph. **15**:185, 1931.

produced by the first, which was usually at the end of the second or third hour. The second dose seemed to have the effect of exploding the charge supplied by the first. Driver and Shaw,[9] likewise, used this method of a divided dose, with excellent results. The amounts of the organisms used by these two authors were equal in the first and second doses. Nelson [8] apparently did not have a standard dosage scheme.

In 1935 Cordes [10] modified the doses of typhoid vaccine used in ophthalmology after two young, and apparently healthy, persons in San Francisco died after intravenous injections of typhoid vaccine for ocular disease. His routine since that time has been to start the treatment with an initial dose of 5,000,000 to 7,000,000 killed typhoid organisms according to the age, size, and general condition of the patient. The following day the dose is increased to from 7,500,000 to 9,000,000 organisms unless there has been a secondary rise of temperature, in which case the second dose is delayed 24 hours. On the third day 9,000,000 to 10,000,000 organisms are given, and on the fourth, 12,000,000 to 15,000,000.

In 1941 Weinberg and Goldstein [11] used typhoid vaccine intravenously in the treatment of neurosyphilis. Among their reasons for choosing typhoid vaccine as the foreign protein for the production of hyperpyrexia were, first, that many of their patients were resistant to malaria and, second, that others were in poor physical condition, a factor which made malarial therapy dangerous. When they first instituted typhoid-vaccine therapy, they used the single-dose method, but the required doses were enormous and the temperature elevations frequently low, so that this method was unsatisfactory. These two authors then decided to use divided doses in much the same way as did Nelson.[8] Through this method they were able to raise the temperature above 103 F. in a great percentage of the occasions on which the vaccine was used. The modification of these authors consisted in using a larger second dose after the first dose of vaccine. The second dose was usually given two hours after the first, provided the temperature had not risen above 103 F. If the reading of the thermometer approximated 103 F. two hours after the first dose was administered, the second dose in the schedule was modified.

In 1942 Solomon and Somkin,[1] while treating patients with subacute bacterial endocarditis with a combination of sulfonamides and hyperpyrexia induced with intravenous injections of triple typhoid vaccine, abandoned the conventional method of obtaining elevations of temperature with a rapid single injection, in favor of a continuous infusion of a saline suspension of the organisms. By this means they obtained striking elevations of temperature. The periods of hyperpyrexia were comparable to those obtained with physical methods, and they were obtained with comparative ease and safety. These authors used the method to produce a high fever, to which they appeared to attribute the beneficial effects of this form of therapy. For their first treatment, they added to 1,000 cc. of sterilized isotonic saline solution triple typhoid vaccine in amounts equal to those ordinarily used in the first of a series of typhoid-shock-therapy injections. This suspension was thoroughly mixed and infused into a vein. The rate of infusion was controlled by increasing or decreasing it according to the reactions of the individual patient, the idea being to

9. Driver, J. P., and Shaw, H. C.: Divided Doses of Typhoid Vaccine in the Fever Therapy of Neurosyphilis, J. A. M. A. **101**:2016, 1933.

10. Cordes, F. C.: Fever Therapy in Ophthalmology, J. A. M. A. **124**:14, 1944.

11. Weinberg, J., and Goldstein, H. H.: Illinois M. J. **79**:139, 1941.

maintain a more or less steady state of hyperpyrexia. To obtain and sustain this, they substituted for the initial suspension replenishing suspensions containing a greater number of killed typhoid organisms, and at times infused a considerable number of bacteria within a short period.

They found that elevations or depressions of the temperature could be obtained within 10 to 25 minutes by increasing or decreasing the rate of flow. They found, also, that once the infusion is discontinued the temperature drops rapidly. Their replenishing suspensions usually contained twice the number of organisms present in the initial suspension.

Each subsequent treatment usually consisted of administering a larger number of organisms than in the preceding one. The elevated temperature was allowed to subside before the next treatment was started. These authors gave as many as 22,000,000,000 killed typhoid organisms in an eight-hour session without ill-effects.

In 1949 Curry and Shaw [2] reported their results with the use of an intravenous infusion containing 1,000,000,000 killed typhoid organisms in the treatment of various ocular diseases. Their method consisted of giving 1,000,000,000 killed typhoid organisms in 1 liter of sterile isotonic sodium chloride solution. The infusion was given at the rate of 20 to 30 drops per minute. Rectal temperatures were recorded at intervals of 15 minutes. If the temperature did not begin to rise in 30 to 45 minutes, the rate of flow was doubled. On the other hand, if the rise in temperature was rapid, the rate of flow was decreased. These authors varied the degree of fever desired from case to case, the height depending on the condition under treatment and the physical state of the patient. In aged or debilitated patients and in patients with notable ateriosclerosis, chilling and hyperpyrexia were avoided by using very slow rates of infusion.

If improvement was not pronounced within 48 hours after the first treatment, a second continuous injection of typhoid vaccine was given. The rate of flow was frequently more rapid with the second treatment. From 50 to 100 mg. of meperidine (demerol®) hydrochloride was given intramuscularly prior to the administration of typhoid vaccine for the purpose of easing the discomforts and unpleasantness of a sustained state of hyperpyrexia.

Because Curry and Shaw [2] wanted to create a state of hyperpyrexia, their method required control of the rate of infusion by increasing or decreasing the latter in an effort to maintain the optimal temperatures. Careful watching of the patient was also demanded by the treatment because of the ever-present risk of too excessive a rise of the temperature, to dangerous levels. All subsequent treatments were identical to the first so far as the number of organisms and method of administration were concerned except that the infusion rates usually had to be faster to obtain a range of fever comparable with that of the previous one.

The method I have used is essentially an elaboration of Curry and Shaw's [2] procedure, the main differences being that 2,000,000,000 killed typhoid organisms are suspended in 1 liter of isotonic saline solution and that the rate of infusion is constant. I do not attempt to create a high state of hyperpyrexia; rather, I keep the temperature at 102 F. or under. The idea was suggested by the commonly observed fact that rapid intravenous injections of typhoid vaccine, which caused a slight rise in temperature, often gave the greatest improvement in a given ocular condition.

MECHANISM OF THERAPEUTIC ACTION

The use of typhoid vaccine, subcutaneously in its earliest stages and intravenously somewhat later, initiated an era in medicine which gave rise to the method of treatment known as nonspecific therapy.

The mechanism of the therapeutic action of typhoid vaccine given intravenously is not yet definitely established. Many explanations and a few theories have been suggested by different investigators.

Allen [3] early expressed the belief that typhoid vaccine either mobilizes the body forces for greater defense or acts as a temporary detoxifying agent, thus allowing the body more time to mobilize its defenses.

Duke-Elder [12] considered it probable that the main effect of typhoid vaccine stems from a general stimulation of the whole mechanism of immunity to greater activity.

In 1935 Brown [13] advanced the concept that foreign-protein injections produce their effects by a nonspecific "interfering" action of the specific antiprotein immune substances. He pointed out that both specific and nonspecific antibodies were produced by foreign-protein injections.

Teague and McWilliams [14] believed that the lymphagogue effect is responsible largely for the therapeutic influence of protein injections, because the antibodies of the blood stream are forced into the lymph spaces and there may destroy invading micro-organisms.

Petersen, Müller, and Boikan [15] concluded that when live or dead bacteria or protein is injected intravenously, the injected material is removed from the blood stream by the cells of the reticuloendothelial system and there "fixed." At the same time, there is a compensatory reversed orientation in the activity of peripheral organs and blood vessels. This is demonstrated by a depression in the metabolic activity of the skin and muscles and a constriction in the peripheral blood vessels. A complete reversal of this state later occurs in both the splanchnic and the peripheral region, and then there is a return to normal equilibrium.

Numerous authors have shown that any form of fever leads to an increase of immune bodies in the circulating blood. It is unknown whether this is due to an increased formation or an increased mobilization of antibodies from the tissues.

In 1914 and 1915 Jobling, Petersen, and Eggstein [16] found that the intravenous injection of bacteria, kaolin, protein split products, and trypsin into experimental animals was almost invariably followed by a more or less pronounced mobilization of serum protease and that similar reactions often occur in patients after the intravenous injection of vaccine and proteoses. These authors also stated that the serum protease is without effect on bacteria, but may be of considerable importance in the

12. Duke-Elder, W. P.: Text-Book of Ophthalmology, Vol. 3, St. Louis, C. V. Mosby Company, 1941, p. 2215.

13. Brown, A. L.: Experimental Uveitis, Tr. Am. Ophth. Soc. **33**:435, 1935; Am. J. Ophth. **20**:583, 1937.

14. Teague, O., and McWilliams, H. J.: Intravenous Vaccine Therapy, J. Immunol. **2**:375, 1917.

15. Petersen, W. F.; Müller, E. F., and Boikan, W.: Reaction of Dog to the Continuous Intravenous Injection of B. Coli, J. Infect. Dis. **41**:405, 1927.

16. Jobling, J. W.; Petersen, W., and Eggstein, A. A.: Serum Ferments and Antiferment After Feeding: Studies on Ferment Action, J. Exper. Med. **16**:34, 1914; **22**:141, 1915.

process of detoxification, since it hydrolyzes protein split products into lower, and nontoxic, forms. The diseased organism thus would temporarily become rid of toxic substances, although the disease process itself and the infecting bacteria might continue to exist.

Petersen [17] demonstrated that during the reaction there is an increase in the content of proteolytic and lipolytic enzymes in the blood. These enzymes break up bacteria and their toxins into harmless products. This phenomenon is accompanied by increased permeability of the cells, whereupon antibodies penetrate into the cells from the blood stream more rapidly. According to Brown,[18] the antibody content of the aqueous is increased, and that of the cornea probably is also increased.

In an effort to study the effect of foreign-protein injections on capillary permeability, Starkenstein, cited by Key,[18] produced corneal ulcers on rabbit eyes and then observed the rate at which dyes would diffuse out at the site of the lesion after a variety of nonspecific injections. His conclusion was that nonspecific injections increase capillary permeability for a short period and later cause a definite lessening of the permeability.

According to Sanders,[19] the intravenous introduction of typhoid vaccine into the body is followed by a prompt effect on the autonomic nervous system: vasodilatation of the splanchnic area; contraction of the peripheral vessels, causing a chill, followed by capillary dilatation; a rise in body temperature, accompanied by a general stimulation of cellular activity; a short period of leucopenia, followed by leucocytosis, in which polymorphonuclear leucocytes predominate, and a rise in antibody content of the blood. The leucocytosis occurs with the onset of the chill and reaches a maximum, and then the leucocyte count gradually returns to normal. Von Szily, cited by Cordes,[10] found that one of the local reactions of the eye consists in active hyperemia of the whole uveal tract, accompanied by infiltration with lymphocytes.

Hench [20] outlined the changes in body physiology which occur during a foreign-protein reaction: (*a*) alterations in basal metabolism; (*b*) peripheral and splanchnic vasomotor changes, including alterations in blood pressure and in the caliber and permeability of arterioles and capillaries; (*c*) alterations in renal function, detectable in output and acidity of the urine, excretion of phenolsulfonphthalein, and concentration of nitrogen, phosphates, urea, uric acid, allantoin and albumin; (*d*) alterations in organic activity, shown by increased flow of lymph, bile, saliva, and breast milk, increased menstrual-flow secretion, and changes in the activity of the liver, gastrointestinal tract, and spleen; (*e*) alterations in the cellular elements of the blood; (*f*) alterations in the fragility of blood platelets, in formation of fibrinogen and in thrombokinase, in coagulation time, and in sedimentation rate; (*g*) alterations in serum ferments, antiferments, antibodies, and the Wassermann reaction; (*h*) alterations in volume, specific gravity, freezing point, and viscosity of the blood; (*i*) alterations in the chemical constituents of the blood involving changes in the

17. Petersen, W. F.: Protein Therapy and Nonspecific Resistance, with an Introduction by Joseph L. Miller, New York, The Macmillan Company, 1922.

18. Key, B. W.: Further Observation of Protein Injections in Severe Ocular Infection, Arch. Ophth. **51**:471, 1922.

19. Sanders, T.: Nonspecific Protein Therapy in Ocular Disease, J. Iowa M. Soc. **31**:51, 1941.

20. Hench, P. P.: Usual and Unusual Reactions to Protein (Fever) Therapy, Arch Int. Med. **49**:1, 1932.

oxygen tension of the plasma, carbon-dioxide combining power, total nonprotein nitrogen of whole blood and serum, sugar tolerance, albumin-globulin ratio, and concentration of urea, uric acid, sugar, fat, total serum protein, and chlorides.

Authorities apparently are divided in their opinion as to which of the above-mentioned physiological changes produce the beneficial effects following foreign-protein injection. While some give importance to the mobilization of enzymes, others maintain that protein injections stimulate the same activities within the body that bacteria stimulate when they invade the body.

The earlier writers on intravenous administration of typhoid vaccine stressed the importance of the fever. According to Barr, Cecil, and DuBois,[21] the injection of typhoid vaccine intravenously is followed by increased heat production, which leads to acceleration of the velocity of chemical reactions.

Darier, cited by Allen,[3] expressed the belief that there is no therapeutic action except it be accompanied by a well-marked febrile reaction. Fradkine, also cited by Allen,[3] stated that there is agreement that the shock is indispensable to therapeutic success.

The belief that the fever was the important factor in this form of therapy apparently led to the development and institution of use of the Hypertherm cabinet.

According to Cecil,[6] it is now assumed that the beneficial effect of the typhoid-vaccine reaction is referable to the fever, and that up to a certain point the higher the fever, the better the results obtained. Therapeutic value is also attributed by some authors to the leucocytosis which accompanies the reaction.

Gifford, cited by Cordes,[10] stated that the fever is the best criterion of the severity of the reaction, because it is the most obvious and most easily recorded manifestation. Although it appears to be the impression that the therapeutic response is directly proportional to the degree of the reaction obtained, one must not overlook the fact that beneficial effects have been reported without the production of appreciable fever. My limited experience bears out this observation. In some of the cases in which the temperature remained around 100 F. the effects obtained were as beneficial as in cases in which the temperature reached 2 degrees (F.) or higher. Zimmer and Buschmann, cited by Cecil,[6] contended that acute conditions frequently necessitate a high-fever reaction, while chronic conditions are often more favorably affected by a low-fever reaction.

Solomon and Somkin[1] expressed the belief that the benefits of intravenous typhoid-vaccine therapy are derived from the hyperpyrexia, increased circulation, stimulation of tissue resistance and antibody formation, and the destruction of lymphocytes, with liberation of their antibodies.

Cordes[10] stated that the role of the fever is still doubtful; it may be only an unimportant manifestation of the reaction, or it may be the cause of the increase in cellular activity. He, however, believed that the vasodilatation is an important part of the beneficial effect derived from this form of therapy. Duggan[22] believed that bacteria, bacterial toxins, and other stimuli associated with infection have the effect of producing local ischemia, which leads to pathologic changes. The relief of vaso-

21. Barr, D. P.; Cecil, R. L., and DuBois, E. F.: Clinical Colorimetry: XXXII. Temperature Regulation After the Intravenous Injection of Proteose and Typhoid Bacillus, Arch. Int. Med. **29**:608, 1922.

22. Duggan, W. F.: Choroiditis Centralis Serosa: Diagnosis, Pathologic Physiology and Therapy, Arch. Ophth. **27**:123, 1942.

spasm with increase of oxygen available to the area seemed rational to him. Gifford and Marquardt [23] pointed out the vasodilator action of typhoid vaccine. This action may explain the beneficial effect of typhoid vaccine in the treatment of acute lesions of the fundus with an angiospastic basis. With these data at hand, it seems reasonable to assume that the vasodilator effect induced by the intravenous injection of typhoid vaccine may be important.

Ricker, cited by Cordes,[10] stated the belief that the underlying mechanism of inflammatory conditions in general is a vascular upset. Bacteria or other stimuli at first set up a vasoconstriction of all terminal vascular segments. The capillaries become fatigued rapidly and relax, producing a fatigue paresis. Thus, dilatation of the capillaries is present, associated with a sustained constriction of the arterioles, resulting in a slowing of the blood stream in the capillary bed. With this dilatation the capillaries become more permeable, possibly owing to anoxemia or to opening up of stroma between the endothelial cells of capillaries. Thus it is apparent that, depending on the degree of slowing of the blood stream, and, therefore, of capillary dilatation, there will develop progressively complex degrees of exudate. In the milder cases this exudate will consist only of plasma and fibrin; in the less mild cases it will contain white blood cells, and in the severe cases it will contain red blood cells. There are many causes for the vasospasm. One of them is the toxins of bacteria. On this basis, an increase of the oxygen to the area by the relief of vasospasm seems proper. The intravenous administration of typhoid vaccine through its sustained vasodilatory action would, therefore, be indicated in such cases.

Recently, Potts, Johnson, Orchen, and Goodman, cited by Dunphy,[24] have pointed out the similarity of the response in cases of uveitis treated with intravenous injections of typhoid vaccine and in those of uveitis treated with corticotropin. In 16 cases of intravenous administration of typhoid vaccine they found without exception the same response as that following corticotropin therapy. They inferred that the good results of intravenous administration of typhoid vaccine are probably due to the stimulation of the adrenal cortex to produce cortisone, through stress reactions acting on the pituitary gland.

According to Cecil,[6] immediately after the injection of typhoid vaccine or any other foreign protein there is initiated the prodromal period of the reaction, which consists of a stage of latency, in which there are no symptoms, and a stage of chill. The latter, which indicates the beginning of the reaction, usually starts one-half to one hour after the injection is given or the infusion is begun. The first symptoms are, therefore, a chilliness or rigor and general aching sensations, similar to the symptoms occurring with the onset of an acute disease. The chill then subsides and is followed by a gradual rise in temperature, which is accompanied with a general cellular activity. With the onset of the fever is initiated the negative phase of the reaction, which represents the period up to and including the maximum rise in temperature. From this point, in the case of the single injection of typhoid vaccine, or from the time the infusion of typhoid vaccine is discontinued, in the case of the method under discussion, until the temperature returns to normal is known as the positive phase of the reaction.

23. Gifford, S. R., and Marquardt, G.: Central Angiospastic Retinopathy, Arch. Ophth. **21**:211, 1939.

24. Dunphy, E. B.: Ocular Therapeutic Principles and Practical Applications, Arch. Ophth. **44**:797, 1950.

Vaughan [25] maintained that "protein poison" was the keystone of the protein molecule and that the fever was due to the parenteral destruction of proteins. He stated that the parenteral injection of bacteria was followed by fever and that this was due to bacterial destruction and splitting up of bacterial protein.

Other symptoms associated with the reaction consist of the usual clinical phenomena of headache, general malaise, mild gastrointestinal disturbances, etc. Although the reaction may seem severe to the patient, the physician will ordinarily consider it mild. Further analysis of the reaction, according to Hench,[20] however, shows notable disturbances in the physical and chemical processes of the body that demonstrate the intensity of the activation of the cellular and humoral defenses. During the negative phase of the reaction there are inaugurated certain phenomena, some of which seem deleterious to the patient's well-being and which, if long-continued, would militate against the usefulness of the treatment. There is in general, however, a sharp reversal of these phenomena at the beginning of the positive phase, and during the reversal, processes of healing are strongly stimulated. It is believed that to obtain a therapeutically positive second phase, there must be an appreciable first phase, and that without the lytic phenomena of the first phase, the healing process, which results from the stimulation of the defensive mechanism of the body, will not be adequate. Changes in organic activity are in general initiated about the time of the chill and are altered in one direction, either increased or decreased, during the negative phase, and in the opposite direction during the positive phase.

Key [18] stated that the side-effects of foreign-protein injection, such as increased irritability, headache, and susceptibility to pain, are due to increased permeability of the nerve cells, associated with lowering of the threshold for nerve impulses.

A focal reaction or activation of the local lesion, immediately after an injection of typhoid vaccine, is a well-recognized, although usually a transitory, phenomenon. According to Hench,[20] it occurs as a result of stimulation of inflammatory foci of infectious origin, of stimulation of inflammatory foci of noninfectious origin, and of stimulation of latent diathetic phenomena. The first of these may occur in ocular infections. Under the second have been grouped ocular and renal lesions, such as nephritic retinitis.

Allergy or anaphylaxis as the cause of focal reactions has been suggested by Kolmer and Gottschalk, according to Hench.[20] Sollmann, cited by Hench,[20] however, has expressed the belief that foreign-protein therapy elicits not an immune, but a pharmacologic, reaction. Some investigators base their claim that true anaphylaxis does not occur on the fact that eosinophilia or bronchial spasm is not in evidence.

The mechanism of the production of focal reactions following the intravenous injection of typhoid vaccine has been outlined by Petersen, as cited by Hench.[20] The injection disturbs the physiological equilibrium. The symptoms of the first phase are increased inflammation, pain, irritability, redness, and swelling at the sites of active or latent inflammation. Four main factors are believed to produce the symptoms. They are (*a*) increased capillary permeability and increased exudation of tissue fluids, resulting in redness and swelling; (*b*) increased tissue pressure and lowered threshold to nerve stimuli, resulting in increased pain and tenderness; (*c*) increased digestion of inflammatory tissue at the foci of circumscribed infection

25. Vaughan, V. C.: Protein Fever: Poisonous Proteins, J. Lab. & Clin. Med. **2**:15, 1916.

and inflammation, and (*d*) marked systemic autointoxication from absorption of digested material if the resultant necrosis of tissue is great.

The departure from the physiologic equilibrium somehow stimulates a reverse phenomenon, which not only restores, but overcorrects, the inflammatory status, and partial or complete healing is obtained. If the lytic phenomena of the first phase are excessive, necrosis may get beyond control, without the healing phenomenon of the second phase to compensate for it. In one case the negative phase may be scarcely obvious, and the positive phase may rule the picture. In another case the opposite may occur, and a positive phase does not seem to follow the negative phase. Then a chronic progression of the inflammatory state may be the deleterious result of protein therapy. Ulceration, even perforation of certain structures, such as the cornea, may occur.

Unusual reactions from the use of typhoid vaccine do occur, but are indeed rare. We have not had any such reaction in the patients we have treated with an infusion of the killed typhoid organisms except in one who had rather severe herpes labialis. The reactions reported include delirium tremens, pneumonia, vomiting, epistaxis, hemiplegia, cardiac dilatation, hematuria, herpes labialis, and death.

Cordes [10] stated that blood chemistry studies indicate that no definite burden is put on the kidneys by the reaction produced by typhoid vaccine, although many minor variations in renal function are produced.

The best results with this form of therapy are obtained when it is given early in the disease, before permanent damage has been done to the involved tissues. It is of greater value in disease of the anterior uveal tract. Cordes [10] and his co-workers have found typhoid-vaccine therapy valuable in the treatment of acute lesions of the fundus when rapid prolonged vasodilatation is desirable. In the past, it has been used in the treatment of phlyctenular keratitis, gonorrheal ophthalmia, interstitial keratitis, corneal ulcer, corneal abscess, acute iritis, chronic iritis, uveitis, postoperative iridocyclitis, and sympathetic ophthalmia. It has also been recommended for retinitis, choroiditis, optic neuritis, and retrobulbar neuritis.

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Annual Reviews

THE ORBIT

Review of Recent Literature

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ORBITAL tumors do not occur frequently in the course of the average ophthalmological practice; yet they never cease to be a source of intense interest and a test of one's diagnostic acumen. Included in Reese's [1] excellent book on tumors of the eye are sections devoted to glioma of the optic nerve and orbit, as well as all the usual and rare malignant growths and lesions simulating them which one is likely to encounter. This text should be consulted whenever one is confronted with lesions in this area. Offret [2] has also written an important book on primary tumors of the orbit and their treatment, with a complete bibliography. He lays stress on the importance of orbital tomography [3] and finds that it may be done alone or in association with an air injection. Air he finds to be the best contrast substance to reveal tumors in the orbit which are transparent to x-rays. Offret classifies the primary orbital tumors as (1) congenital tumors, of which the epidermoid cysts are the most frequent; (2) nerve tumors (peripheral glioma, glioma of the optic nerve, orbital meningioma; (3) vascular tumors (intermittent orbititis, pulsating exophthalmos, orbital angioma); (4) bony tumors; (5) epithelial tumors (lacrimal tumor, cylindroma), and (6) benign or malignant conjunctival tumors. In an important chapter on treatment, he lays stress on the necessity of treating surgically most tumors amenable to eradication, not through the anterior but through the temporal, route and, in certain forms, the intracranial route. The author concludes that it is necessary to make a precise anatomoclinical diagnosis in all cases and that exploratory orbitotomy followed by biopsy is the best method when doubt exists as to the real nature of the lesion.

Jackson,[4] on the other hand, feels that the malignant tumors of the orbit, whether epiblastic or mesoblastic, are little affected by surgical intervention and that surgery, therefore, has little to offer. He states that the only malignant growth for which radical surgery is indicated is the retinoblastoma. He believes that malignant tumors, on established proof, should be submitted to deep x-ray therapy without further surgical intervention.

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1. Reese, A. E.: Tumors of the Eye, New York, Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 1951.

2. Offret, G.: Primary Tumors of the Orbit and Their Treatment, Paris, Masson & Cie, 1951.

3. (*a*) David, M.; Fischgold, H.; Bregeat, P.; Tolairach, J., and Fissore, A.: Roentgen Tomography of Tumor Pressure in Unilateral Exophthalmos, Rev. neurol. **83**:379-386, 1950. (*b*) Petit-Dutaillis, D., and Fischgold, H.: Roentgen Tomography in Unilateral Exophthalmos, ibid. **83**:386-387, 1950. (*c*) Fischgold, H.; Prot, D., and Fissore, A.: Unilateral Lesions of the Anterior Clinoid Process in Neoformations of the Sphenorbital Region, Presse méd. **59**:400-402, 1951.

4. Jackson, H.: Orbital Tumours, Ann. Roy. Coll. Surgeons England **9**:123-140, 1951.

Spaeth [5] made a statistical analysis of 170 consecutive cases of ocular tumor seen during the 10-year period from 1940 to 1950 in Philadelphia. He concludes that patients with sarcoma die early in life and early in the course of the disease. He finds adenocarcinoma the most malignant of all the epithelial-cell tumors of the eye.

Davies [6] advises that if there is evidence of orbital extension of malignant tumor, he prefers enucleation followed by the insertion of a radium bomb to exenteration of the orbit. In the case of unilateral retinoblastoma, he believes that intracranial section of the optic nerve distal to the chiasm, followed by enucleation in about two weeks, is the preferable course.

Jackson finds that most patients with orbital tumor initially complain of an ocular disturbance, such as protrusion of the eye, disturbed vision, restricted motility, diplopia, or pain. Pathologically, in no series of cases recorded could he find any relative incidence available. He does not think that malignant disease is common or that metastatic malignant growths are frequent in the orbit. He finds the most common orbital lesion to be a chronic infectious granuloma. Other deductions which he was able to make from his studies are as follows: 1. An optic nerve tumor in a child is usually gliomatous, whereas in an adult it is usually a meningioma. 2. Unilateral proptosis without other patholgic sign of endocrine disorder is usually due to tumor. 3. When retraction of the upper eyelid is present, tumor is rarely found.

Orbital tumors vary so much in the manner of appearance that they continue to stimulate physicians to write about the peculiarities encountered in the hope that others may be helped when faced with a similar problem. Bonnet [7] describes a case in which attacks of pain were accompanied by flashes of light in the left eye. At first no cause of the symptoms could be found, since the fundus was normal and there were no orbital signs. Vision decreased with the attacks, and only later was choroiditis found. The choroiditis progressed in spite of treatment to development of edema of the disk and exudative detachment of the retina. These inflammatory reactions subsided with x-irradiation, but a year later pain and uveitis and glaucoma developed, to cause loss of vision. Although proptosis was noted before the onset of the visual symptoms, a palpable orbital mass was not discovered for three years. Orbital exenteration revealed the presence of malignant melanoma which had invaded the optic nerve, but not the interior of the eye, causing visual loss and orbital involvement rather than prominent intraocular involvement.

A case of carcinoma of the orbit is described by Sapuppo,[8] which he states is the third mentioned in the literature (van der Hoeve; Happe). The patient, a man of 41, underwent exenteration of the orbit. The tumor was diagnosed histologically as basal-cell carcinoma. The possibility of its being a metastatic lesion from a

5. Spaeth, E. B.: Ocular Tumors: A Study of Incidence of the Various Types and Their Mortality Rates, A. M. A. Arch. Ophth. **46**:421-423, 1951.

6. Davies, C. E.: Modern Methods for Treatment for Malignant Tumours of the Eye, Canad. M. A. J. **62**:568-571, 1950.

7. Bonnet, P.: A Rare Clinical Form of Orbital Tumor: The "Ocular" Form, Arch. opht. **11**:329-332, 1951.

8. Sapuppo, C.: Primary Carcinoma of the Orbit, Gior. ital. oftal. **4**:108-113, 1951.

primary tumor elsewhere being excluded, there remained the possibility that it might be of primary endorbital origin, from aberrant embryonic cells in the orbital tissue.

Another rare tumor of the orbit was described by Minicucci,[9] an intraorbital giant-cell tumor originating in the periosteum of the medial wall of the orbit. Histologically, this tumor consisted of round and spindle cells and of numerous multinucleated giant cells. The fibrillary stroma was loose, and its wide interstitial spaces were filled with an amorphous substance. Though frequent in other parts of the body, this type of tumor is rarely to be found in the orbit, only five cases being described in the literature.

Beller and Kornblueth [10] point out the characteristic features of eosinophilic granulomatous tumors as they appear in the orbit. Most cases occur in the first two decades of life. The tumor is commoner in males than in females and often follows trauma. Rapid increase in size is usual, and roentgenographic appearances suggest bone erosion. In most cases blood and bone-marrow eosinophilia are noted. The authors emphasize that this condition should be considered in the differential diagnosis of a space-occupying orbital lesion, especially when bony erosion has occurred. The condition is usually not mentioned as one of the causes of proptosis from tumor of the orbit. A roentgenogram of the bone as a rule shows a well-defined osteolytic process with little evidence of reactive bone formation at the margin of the defect. In his case the lesion was removed piecemeal by means of a curet, and later deep x-ray therapy, in a dose 2,150 r, was given. Babel [11] recommends trial with antibiotics and concludes that the lesions are probably infectious in origin.

A rare type of Recklinghausen's disease (neurofibromatosis) of the orbit in a premature infant is reported by Prendergast.[12] There was hypertrophy of the upper lid with proptosis of the globe. Deep central keratitis and vascularization of the iris were present. The pupil reacted only slightly to light, and the intraocular tension was 39 mm. X-ray studies showed enlargement of the left orbit and infraorbital fissure with displacement of the lesser wing of the sphenoid bone. A biopsy specimen, obtained through a Krönlein approach, showed a plexiform neuroma involving the ophthalmic and maxillary divisions of the fifth cranial nerve. Avello [13] advises that in all cases of suspected tumor of the orbit the physician make a complete study of the patient in order to detect the presence of a concealed form of this phacomatosis in the form of pigmentary or psychosomatic disturbance.

THYROTOXIC AND THYROTROPIC EXOPHTHALMOS

A profusion of articles have appeared during the past few months on the endocrine forms of exophthalmos. A great many of the articles merely reiterate the well-known theories of the formation of the exophthalmos and the accepted

9. Minicucci, G.: Giant-Cell Tumor in the Orbit, Riv. oto-neuro-oftal. **26**:222-232, 1951.

10. Beller, A. J., and Kornblueth, W.: Eosinophilic Granuloma of the Orbit, Brit. J. Ophth. **35**:220-225, 1951.

11. Babel, J.: A Rare Form of Orbital Tumor, Eosinophile Granuloma, Arch. opht. **11**:35-38, 1951.

12. Prendergast, J. J.: Congenital Tactile Corpuscle Neuroma of the Orbit and Antrum: A Rare Oculo-Facial Manifestation of von Recklinghausen's Disease, Tr. Pacific Coast Oto-Ophth. Soc. **31**:117-125, 1950.

13. Avello, J.: Exophthalmos Due to Meningioma in Patient with Recklinghausen's Disease, Arch. Soc. oftal. hispano-am. **11**:179-185, 1951.

therapy. On searching the literature, Saltzman and Mellicker [14] found eight cases in which exophthalmos preceded all clinical and laboratory manifestations of thyrotoxicosis. To this list the authors added a case in which there was an interval of 20 months between the appearance of unilateral exophthalmos and the onset of thyrotoxic symptoms. Bedrossian [15] emphasizes the difficulty encountered in arriving at an early diagnosis of unilateral exophthalmos when the underlying pathological condition is of endocrine origin. He points out that unilateral exophthalmos may later become bilateral, and even go on to require Naffziger decompression.

Radnót [16] writes that malignant exophthalmos usually starts at the time of decreased thyroid and gonadic activity and that, therefore, thyroidectomy and thiouracil treatment should be applied cautiously during the climacteric. In investigating the effect of the steroid hormones on exophthalmos, Smelser and Ozanics [17] made the following observations: 1. Removal of the gonads neither enhanced nor inhibited the occurrence or degree of the exophthalmos. 2. Administration of androgen (testosterone) did not affect the degree of experimental exophthalmos. 3. Administration of adrenocortical hormone (desoxycorticosterone, or adrenal cortex extract) did not influence the exophthalmos produced in guinea pigs. 4. The orbital contents were definitely reduced in control guinea pigs treated with estrogen. 5. Estrogen (estradiol) administration caused marked regression of the experimentally produced exophthalmos, and the orbital contents, including the orbital fat, were reduced in weight in these animals. The findings of the authors indicate that the effect of the estrogen was primarily upon the orbital tissue, rather than on the interaction of the pituitary hormone and the orbital tissue, which caused the exophthalmos. Although Weekers and Dedoyard [18] have not found any good effect in endocrine exophthalmos from administration of estrogen or thyroid extract, irradiation of the pituitary gland, or other medication reported to decrease the activity of the anterior lobe of the pituitary, François [19] has found estrogen therapy useful and recommends the giving of large doses of estrogens, as he considers that they diminish the activity of the anterior lobe.

Beierwaltes,[20] and Paufique, Papillon, and Guinet [21] give detailed observations based on careful clinical histories of patients suffering from malignant exophthalmos and followed over long periods who responded satisfactorily to a combined course

14. Saltzman, S. L., and Mellicker, M. C.: Unilateral Exophthalmos as a Forerunner of Thyrotoxicosis, Am. J. Ophth. **34**:372-374, 1951.

15. Bedrossian, E. H.: Unilateral Thyrotropic Exophthalmos, Am. J. Ophth. **4**:727-732, 1951.

16. Radnót, M.: Exophthalmos of Endocrine Origin, Orvosi hetil. **92**:380-384, 1951.

17. Smelser, G. K., and Ozanics, V.: Relation of Steroid Hormones to the Development of Experimental Exophthalmos, Am. J. Ophth. **34**:87-94, 1951.

18. Weekers, R., and Dedoyard, J.: Exophthalmos of Endocrine Origin, Bull. Soc. belge opht. **97**:122-137, 1951.

19. François, J.: Estrogen Therapy in Graves's Disease, Bull. Soc. belge opht. **97**:194-216, 1951.

20. Beierwaltes, W. H.: Irradiation of the Pituitary in the Treatment of Malignant Exophthalmos, J. Clin. Endocrinol. **11**:512-530, 1951.

21. Paufique, L.; Papillon, J., and Guinet, P.: Radiotherapy of Edematous Exophthalmos Without Hyperthyroidism, J. radiol. et électrol. **32**:21-26, 1951.

of x-rays and hormone therapy. Beierwaltes was under the impression that real improvement did not become manifest until pituitary irradiation was given and that the average onset of recession of the proptosis was 3 months and the average maximum recession 12 months. Paufique and associates consider a combined course of x-rays and hormonal therapy (using thyroxine and estrogens mainly) the treatment of choice in all except the milder cases of recent onset, in which hormonal therapy alone may suffice. The authors feel that surgery should be reserved as a last, desperate measure for very advanced cases with complications, such as corneal ulceration or perforation.

Paufique and associates cite two factors of importance relative to x-ray therapy, namely, (1) that both orbits, as well as the region of the pituitary gland, should be irradiated, and (2) that for the achievement of success relatively large doses (of the order of 4,000 r) are necessary. The technique of treatment used was briefly as follows: Two temporal fields, 5 by 8 cm., were so placed as to include the orbits as well as the pituitary gland. These fields were, in some cases, supplemented by two direct anterior orbital fields. The total dose given varied from 2,000 to 5,000 r, 200 r at 170 kw. being given to two fields three times a week. The prognosis, which is stated to be more favorable in men than in women, appeared to depend largely on the duration of symptoms, the degree of disability, and the severity of the associated complications. In discussing the mode of action of roentgen therapy in this condition, the authors suggest a twofold effect, namely, (1) a neuroendocrine effect on the diencephalohypophyseal region and (2) a local vasomotor effect, acting directly on the intraorbital edema and bringing about improvement in the local hydrostatic equilibrium.

It is disappointing that Woods [22] and Fitzgerald and associates [23] obtained such equivocal results from treatment of malignant exophthalmos with corticotropin (ACTH) and cortisone. Wolfson and his associates [24] were able by administration of corticotropin or cortisone to induce thyroid depression and good clinical improvement in 5 of 11 patients with frank hyperthyroidism due to diffuse hyperplasia (Graves's disease). Relapse apparently often follows cessation of treatment. They found considerably less satisfactory results in similar studies on 10 patients with malignant exophthalmos. Several patients had relief of ocular pain, lacrimation, or chemosis, but only one obtained a really sastifactory improvement in proptosis. The authors suggest that their observations indicate that the hyperactive pituitary believed implicated in these clinical disorders of the thyroid-pituitary system is less easily restrained by increased glycocorticoid levels than is the normally functioning thyroid-pituitary axis.

22. Woods, A. C.: Present Status of ACTH and Cortisone in Clinical Ophthalmology, Am. J. Ophth. **34**:945-960, 1951.

23. Fitzgerald, J. R.; Bellows, J. G.; Donegan, J. M.; Gamble, R. C.; Krause, A. C.; Mann, W. A.; Pearlman, M. D., and Zekman, T. N.: Early Clinical Results of ACTH and Cortisone Treatment of Ocular Disease, A. M. A. Arch. Ophth. **45**:320-333, 1951.

24. Wolfson, W. Q.; Beierwaltes, W. H.; Robinson, W. D.; Duff, I. F.; Jones, J. R.; Knorpp, C. T.; Siemienski, J. S., and Eya, M.: Corticogenic Hypothyroidism: Its Incidence, Clinical Significance and Management During Prolonged Treatment with ACTH or Cortisone, in Mote, J. R., Editor: Proceedings Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, Vol. 2, 1951.

The only new theory propounded on the influence of thyrotropic hormone on connective tissue was that of Asboe-Hansen and Iversen,[25] who injected subcutaneously large doses of thyrotropin into guinea pigs, with resulting general fat mobilization and an accumulation of fat in the liver, muscles, and kidneys within 24 hours. By means of a special histochemical technique, the authors demonstrated accumulations of mast cells and hyaluronidase-sensitive mucopolysaccharides in the connective tissue at various sites, most prominent in the retrobulbar tissue, of guinea pigs treated with thyrotropin. They postulate that since mucopolysaccharides, particularly hyaluronic acid, are known to possess a striking capacity to bind water, an increased content of these substances may explain the protrusion of the eyes.

MISCELLANEOUS ORBITAL AFFECTIONS

Hemorrhagic disease of the newborn presenting as unilateral proptosis is a disease first described by Minot in 1852 and named by Townsend in 1894. Kessel and Williams [26] state that it is characterized by an unusual tendency to spontaneous and prolonged bleeding during the first week of life, usually from the second to the fifth day. The authors present two cases in which unilateral hemorrhage behind the eye was the only manifestation of the disease. The proptosis, after a few days, became less marked and in one case had completely disappeared by the end of the third week. The prothrombin index was low, and the prothrombin time was raised. Administration of synthetic vitamin K seemed to have a beneficial effect.

Bilateral exophthalmos in the newborn following spontaneous delivery is found by Kundert [27] to be a rare occurrence. Fracture of the orbit with strangulation of the opthalmic vein in the superior orbital fissure, retrobulbar hemorrhage, subperiostal hemorrhage, and cavernous-sinus injury have been considered etiologic factors in the three or four previously reported cases. Trauma produced by molding of the head during its passage through the birth canal was believed to be the primary factor in all cases. Protection of the corneas from exposure keratitis is of paramount importance.

Acute inflammation of the orbit includes inflammation of the periocular and retro-ocular tissues. Among the causes Grom [28] lists trauma, infectious diseases, sinusitis, dental infections, styes, Meibomian cysts, and furuncles of the upper lip or the nose. According to the Birch-Hirschfeld statistics, acute inflammation was the cause of death in 12.7% of cases. The authors believe that antibiotics (mainly penicillin) have brought decisive changes in the therapy and prognosis of acute orbital inflammation. Marin Enciso [29] is of the opinion that early orbitotomy, combined with the administration of sulfonamides and antibiotics, is recommended in the treatment of orbital sepsis.

25. Asboe-Hansen, G., and Iversen, K.: Influence of Thyrotropic Hormone on Connective Tissue: Pathogenetic Significance of Mucopolysaccharides in Experimental Exophthalmos, Acta endocrinol. **8**:90-96, 1951.

26. Kessel, I., and Williams, C. G.; Hemorrhagic Disease of the Newborn Presenting as Unilateral Proptosis, S. African M. J. **25**:126-127, 1951.

27. Kundert, K. F.: Bilateral Exophthalmos in the Newborn, Am. J. Ophth. **34**:1173-1175, 1951.

28. Grom, E.: Acute Inflammation of the Orbit, Arch. Soc. oftal. hispano-am. **11**:241-251, 1951.

29. Marin Enciso, E.: Early Orbitotomy in Orbital Sepsis, Arch. Soc. oftal. hispano-am. **10**:971-975, 1950.

Walsh and Hedges [30] investigated hemorrhages in the optic nerve sheath from the standpoint of their relation to intracranial hemorrhages and conclude that such hemorrhages do not originate as a result of forward passage of blood from the intracranial meningeal spaces. They established to their satisfaction that there is little, if any, extension of hemorrhage via the optic canal. They state their opinion that optic-nerve-sheath hemorrhages originate in rupture of veins or venous channels in the dura and that the degree and extent of venous ruptures are dependent on the rapidity of onset and the magnitude of elevation of venous pressure in the brain or obit. Manschot,[31] however, disagrees with the view of Walsh and Hedges that these hemorrhages can be explained only by a sudden rise of intracranial pressure, causing stasis in all the venous channels which drain the tissues of the eye and the contents of the orbit. He states that these authors have forgotten that there are many anastomoses of the veins in the orbit with the facial vein (supraorbital, angular, deep facial, and pterygoid plexus). He states that it is clear that a sudden rise in the intracranial pressure can never produce a stasis in all the venous channels which drain the tissues of the eye and the contents of the orbit. He thus does not agree with their conclusion that the transmission of increased venous pressure from the cranial cavity to the orbital veins is established or that the degree and extent of venous ruptures are dependent on the rapidity of onset and the magnitude of elevation of venous pressure in the brain and orbit. Since small recurrent branches pass back through the superior orbital fissure or run back in the dural sheath of the optic nerve, arterial overfilling rather than venous stasis can, in his opinion, more satisfactorily explain the hemorrhages throughout the whole orbit, since the acute plethora of the ophthalmic artery refers also to the central retinal artery and its other branches in the orbit.

The correct diagnosis of fibrous dysplasia of the orbital bones in unilateral proptosis was made by x-rays in 25 to 40% of the cases presented by King and Hayes.[32] They recommend a surgical approach directed toward total excision of the involved bone through frontal craniotomy. The optic foramen and orbital plates are decompressed at the same time. An even higher percentage of correct diagnoses are made in the case of osteitis deformans (Paget's disease) of the skull with orbital involvement. Montresor [33] reports the case of an elderly patient showing osteitis deformans which produced marked optic atrophy in the right eye and papilledema in the left eye. These changes were caused by narrowing of the optic foramina, which was roentgenologically demonstrated. To forestall optic atrophy in the left eye, trepanation of the superior wall of the left optic canal is suggested.

Cowan [34] uses the term "pseudotumor" to refer to any tumor of the orbit which is not a true neoplasm, e. g., carcinoma or cylindroma. He refers to Reese's paper

30. Walsh, F. B., and Hedges, T. R., Jr.: Optic Nerve Sheath Hemorrhage, Am. J. Ophth. **34**:509-526, 1951.

31. Manschot, W. A.: Optic Nerve Sheath Hemorrhage, Am. J. Ophth. **34**:1335-1336, 1951.

32. King, R. B., and Hayes, G. J.: Unilateral Proptosis Due to Fibrous Dysplasia of Bone: Report of Two Cases, A. M. A. Arch. Ophth. **46**:553-559, 1951.

33. Montresor, D.: Foster Kennedy Syndrome in Paget's Disease of the Skull, Ann. ottal. e clin. ocul. **77**:343-352, 1951.

34. Cowan, T. W.: Orbital Pseudotumors, A. M. A. Arch. Ophth. **46**:390-402, 1951.

in which 50% of 30 cases of orbital masses removed at exenteration of the orbit for supposed primary neoplasm are listed as a chronic inflammatory tissue mass. This paper is too involved for abstracting but should be read in the original as an aid in the differential diagnosis of this condition.

Tassman,[35] in writing of the orbital apex-sphenoidal fissure syndrome, states that the bony changes in the orbital apex produce pressure on the structures which pass through the sphenoidal (superior orbital) fissure and the optic canal. He gives inflammation of the bones of the orbit arising from pathological conditions of the sinuses as a common cause, but malignant disease is even commoner. A malignant growth, however, is usually far advanced when brought to the attention of the ophthalmologist. Ptosis and ophthalmoplegia are the most important and earliest signs. The patient is usually 60 years of age or over and complains of recurrent epistaxis and nasal symptoms.

Lereboullet and Pluvinage[36] write interestingly on the sphenoidal fissure-cavernous sinus syndrome and classify it as follows: 1. The sphenoidal fissure syndrome is characterized by symptoms caused by lesions of the oculomotor nerves, the ophthalmic branch of the fifth cranial nerve, and the optic nerve. There is associated exophthalmos in the case of tumor. 2. The syndrome of the orbital apex (Rollet's syndrome) is considered nowadays as a pure syndrome of the sphenoidal fissure, leaving intact the optic nerve. There is nearly always exophthalmos, due to its customary tumor origin. 3. The syndrome of the external wall of the cavernous sinus is characterized by unilateral ophthalmoplegia plus a lesion of the ophthalmic branch of the fifth nerve. The difference between this syndrome and the sphenoidal-fissure syndrome is that in the former the ocular paralysis begins with the sixth nerve, whereas in the latter it begins with the third nerve. On the other hand, in the former the ophthalmic lesion is characterized by neuralgia, whereas in the latter there is no pain. Furthermore, according to Jefferson, there are three types of syndromes of the external wall of the cavernous sinus, depending on the site of the lesion (syndrome of the posterior section, syndrome of the middle section, and syndrome of the anterior section). The authors think that the definition of the so-called syndrome of the sphenoidal fissure should be revised and that the clinical differentiation can be made as follows: If the symptoms are predominantly dependent on the fifth nerve, the lesion is located at the level of the cavernous sinus; if, on the contrary, the principal symptom is exophthalmos associated with a lesion of the optic nerve, the process is located in the posterior pole of the orbit. They thus think that it is better to consider the various types of syndromes described above as one syndrome exclusively, and they call it the sphenocaverous syndrome of Clovis Vincent. They state that the main etiologic factors are trauma; infectious processes, such as tuberculous and syphilitic osteomyelitis; malignant growths at the base of the skull; meningioma of the lesser wing of the sphenoid bone, arachnoiditis, and aneurysm of the carotid artery.

35. Tassman, I. S.: Orbital Apex-Sphenoidal Fissure Syndrome, Am. J. Ophth. **34**:762-763, 1951.

36. Lereboullet, J., and Pluvinage, R.: Sphenocavernous Syndrome: Its Classification, Etiology, and Definition, Riv. oto-neuro-oftal. **22**:644-648, 1950.

VASCULAR LESIONS INVOLVING THE ORBIT

The cavernous-sinus syndrome is clinically a well-defined picture in which the third to the sixth cranial nerve are affected simultaneously. Huber [37] states that, depending on the degree of damage to the trigeminal nerve, the syndrome may be divided into three types: (1) the posterior syndrome, affecting the whole of the fifth nerve; (2) the medial syndrome, affecting the first and second divisions of the fifth nerve, and the fourth (trochlear) and sixth nerves, and (3) the anterior syndrome, with damage only to the ophthalmic, fourth, and sixth nerves. The author finds that in the first two divisions there may be slight exophthalmos, and usually ptosis and internal ophthalmoplegia. Large aneurysms may also damage the homolateral optic nerve. Sometimes the trigeminal pain disappears, leaving hypesthetic or anesthetic zones. He states that the diagnosis may be made clinically, by x-rays, or by filling of the aneurysm as seen by arteriography.

Spontaneous recovery from pulsating exophthalmos after bilateral aseptic thrombosis of the cavernous sinus is indeed a rare and happy occurrence, a case of which is reported by Knudtzon.[38] There were no signs of inflammation.

Sugar and associates [39] find that spontaneous thrombosis of the carotid arteries is usually due to arteriosclerosis, and more rarely to obliterative syphilitic arteritis, embolism, or nonsyphilitic arteritis. They find that sclerosis of the carotid arteries has been reported even in young adults. They think it reasonable to assume that the thrombosis usually ascends from the atheromatous carotid complex, but the reverse is shown to be possible in their case report. The symptoms of thrombosis of the carotid arteries are manifold in hemiparesis, speech defects, temporary blindness, nystagmus, and diplopia. Thrombosis of the central retinal artery and optic nerve atrophy has been described. While the condition may occur without visual symptoms, the paper is concerned with cases in which these symptoms are present. In the three cases reported there was complete or partial optic atrophy, which was caused by occlusion of the central retinal artery when unilateral, and was probably due to involvement of the nutrient arteries of the optic nerve in a case of bilateral optic nerve atrophy.

Teitgen and Benedict [40] give a good discussion of the vascular lesions of the orbit which cause proptosis. They found ecchymosis of the lids and conjunctiva in all cases in which there were recurrent episodes. The exophthalmos may be intermittent, recurrent, or permanent. The primary surgical difficulties encountered in either the transcranial or the anterior approach were bleeding and collapse of the tumor during operation, making removal almost impossible.

CONGENITAL ANOMALIES OF ORBIT

Surveys in institutions for the blind as to the cause of blindness have repeatedly revealed that congenital anomalies are now largely responsible for the blindness. This finding has led to increasing interest in such anomalies, and efforts will be

37. Huber, A.: The Cavernous Sinus Syndrome, Ophthalmologica **121**:118-125, 1951.

38. Knudtzon, K.: A Remarkable Case of Pulsating Exophthalmos in an Old Patient Who Recovered Spontaneously After Bilateral Aseptic Thrombosis of the Cavernous Sinus, Acta ophth. **28**:363-369, 1950.

39. Sugar, H. S.; Webster, J. E., and Gurdjian, E. S.: Ophthalmologic Findings in Spontaneous Thrombosis of the Carotid Arteries, Arch. Ophth. **44**:823-832, 1950.

40. Teitgen, R. E., and Benedict, W. L.: Venous Aneurysms of the Orbit, Am. J. Ophth. **34**:94-98, 1951.

made to reduce this incidence. Moffie [41] found four generations in which a presumably dominant oxycephaly was accompanied (sometimes in the same person) by syndactylism, epilepsy, or paralysis of the ocular muscles.

In describing the developmental mechanism of acrocephalosyndactylism, Degenhardt [42] states the belief that the abnormal development leading toward brachysphenacrocephaly makes its first appearance between the 29th and the 35th day of embyonic life. The same holds true for the different types of syndactylism. The syndrome differs from dysostosis craniofacialis (Crouzon) in its earlier time of determination.

Achelis [43] found an instance in which a child was born with right anophthalmos after an attempted induction of abortion in the second month of pregnancy. The full-term infant showed as well an extensive lesion in the temporal region, which was only partly healed at birth. A dermoid cyst was found under the healed part of the defect.

As more congenital anomalies of the orbit are studied, it is only logical that new theories of their development will arise. Morton [44] states that it is now believed that cyclopia results from failure of the central optic field in the primitive forebrain to develop into a central chiasmatic region, separating the two laterally placed eyes, rather than that, as was formerly supposed, there was a secondary fusion of two originally separate optic primordia. He believes that one or more factors act adversely on the anterior end of the neural plate, affecting particularly the development of the optic field, so that the median raphé, rather than the lateral parts of the field, go on to form an eye.

At times the usual characteristics of gargoylism are not present at birth or for several months later. This becomes especially important in cases in which adoption of very young infants is contemplated. This is exemplified in Wagner's [45] article on dysostosis multiplex with maldevelopment of Bowman's membrane. When the child came under observation, at the age of 3 months, few of the characteristic symptoms had developed, and the bone changes then found might well have been rachitic. Later, all the usual symptoms developed, until, at the age of about 1 year, the child showed the full picture of gargoylism, including corneal opacities. The child died at the age of 2 years, after a herniotomy, and necropsy confirmed the clinical findings. Histologically, there was almost complete absence of Bowman's membrane. Wexler,[46] in writing on the ocular histology in gargoylism (Hurler's disease) paints the clinical picture as that of dwarfism with deformity of the limbs and enlargement of the liver and spleen. The head is large; the orbits are wide apart, and the root

41. Moffie, D.: A Family with Oxycephaly and Acrocephalosyndactylism, Rev. neurol. **83**:306-312, 1950.

42. Degenhardt, K. H.: The Development Mechanism of Acrocephalosyndactylism, Ztschr. menschl. Vererb.- u. Konstitutionslehre **29**:791-819, 1950.

43. Achelis, E.: Anophthalmos Following Attempted Induction of Abortion, Med. Klin. **45**:1214-1215, 1950.

44. Morton, W. R. M.: Cyclopia, Brit. J. Physiol. Optics **8**:65-72, 1951.

45. Wagner, F.: Dysostosis Multiplex (Gargoylism) with Maldevelopment of Bowman's Membrane, Ztschr. Kinderh. **69**:179-190, 1951.

46. Wexler, D.: Ocular Histology in Hurler's Disease (Gargoylism), A. M. A. Arch. Ophth. **46**:14-21, 1951.

of the nose is broad and depressed. The neck is very short; the spine is kyphotic, and the belly is protuberant. In over 75% of the cases there is a clouding of the corneas, which in the early stages appears to be located in the deeper layers of the corneal stroma. Later the opacity becomes diffuse, involving all the layers except the epithelium and endothelium. The author finds, in addition, similar, but more extensive, disease of the scleral tissue, as well as widespread infiltration of the arachnoid sheath of the optic nerve with typical foam cells.

An interesting observation has been made by Hudelo,[47] who, from studies of 25 cases of malformations of the superior maxillary arch characterized by marked narrowing of the upper jaw with projecting incisor teeth, pointed palatal arch, and diminished vertical diameter of the orbit, showed that these deformities may be responsible for astigmatism with the rule. He claims that successful orthodontic treatment may lessen the astigmatism.

An unusual congenital cyst of the optic nerve with encephalocele is described by Dvorak-Theobald and Middleton.[48] These authors find that the encephalocele is a prolapse or hernia of the meninges with cerebrospinal-fluid contents, including the brain substance prolapsing within the meningeal sac through an opening in the skull wall. The bony defect is usually within the line of suture, and rarely a posterior-orbital meningocele, or encephalocele, presents near the apex of the orbit.

The preformed openings through which encephaloceles of the posterior part of the orbit may penetrate are the optic foramen, the sphenoidal (superior orbital) and sphenomaxillary fissures, and the posterior ethmoidal foramen. Openings are usually unilateral and may affect all openings, or any one. The nonpreformed openings may be congenital deficiencies, traumatic defects, or defects caused by preexisting or concurrent disease. The dura mater is usually not involved except in the very early stages, when it bursts, allowing the soft tissues to herniate. The authors present an unusual picture of a congenital cyst interposed between the optic nerve and its arachnoid sheath on the nasal side, and extending into the posterior part of the globe through a defect in the sclera. Within the cyst are strands of tissue having the appearance of normal brain tissue.

A receding jaw and a large mouth are frequently signs of the incomplete mandibullofacial dysostosis syndrome, while deformities of the external and middle ear, malformations of the lids, such as colobomata and ptosis, and abnormalities of head contours, such as bird head, are less frequent, according to the impressions of Roussel.[49] He finds that at about the seventh week of embryonic life defective development in the first and second branchial arches causes imperfections of the lower part of the face. The author reports cases from four successive generations in a family predisposed to mandibulofacial dysostosis by irregular dominant heredity. Each succeeding generation had more manifestations, and in the fourth generation a case of the complete syndrome appeared.

47. Hudelo, A.: Astigmatism and Malformations of the Superior Maxillary Arch., Ann. ocul. **184**:522-530, 1951.

48. Dvorak-Theobald, G., and Middleton, W. H.: Congenital Cyst of the Optic Nerve with Encephalocele, Tr. Am. Acad. Ophth. **55**:277, 1951.

49. Roussel, F.: Mandibulofacial Dysostosis, Ann. ocul. **184**:788-802, 1951.

ORBITAL TRAUMA

Anthony [50] describes a method of treating recent depressed fractures of the orbital floor by a water balloon in the antrum of Highmore (maxillary sinus), and of treating healed fractures by refracturing the floor of the orbit and raising it with a metal jackscrew placed in the sinus and introduced through a Caldwell-Luc incision in the canine fossa. In other cases the contusion to the orbital margin may appear slight and may not be accompanied by external or fundal evidence of damage for several hours, Haemmerli [51] reports that optic nerve lesions may be the result of a crack in the optic canal, or they may be due to hemorrhage in the nerve sheath or into the optic nerve itself or to damage of the nerve in the optic canal by the coup and contrecoup of the brain, and result in the delayed appearance of otpic-nerve congestion, field changes, and visual loss.

List [52] found it necessary to do a lateral decompression of the orbit and removal of the hematoma produced by orbital and skull fracture because of the presence of increasing exophthalmos, visual impairment, papillitis, extraocular paralyses, and severe headache. He warns of the necessity of differentiating this condition from vascular lesions and cellulitis but states that when the diagnosis is made, early, conservative treatment is advisable.

In reviewing the ocular injuries in boxers, Favory and Sédan [53] note particularly the frequency of orbital hyperostoses and wounds of the brows, cornea, and iris, and the relative rarity of cataract and glaucoma. They consider that retinal hemorrhage is frequent and causes retinal separation.

LESIONS OF THE LACRIMAL GLAND AFFECTING THE ORBIT

Wilson [54] discusses the differential diagnosis of acute unilateral dacryoadenitis and notes that tenderness over the malar bone, below and behind the outer canthus, may be a valuable diagnostic sign in the early stages in which swelling renders palpation of the gland impossible. In all his cases, infection of the respiratory tract preceded the glandular infection. He finds that use of penicillin and sulfonamides results in resolution in the majority of cases, and that only rarely is it necessary to resort to surgical evacuation of pus from the orbit.

Sjögren and Kronning [55] agree with Spaeth that extirpation of the lacrimal gland because of epiphora is simply the substitution of a dry eye for a wet eye, and that the former of the two evils is by far the worse. They think it is doubtful whether the procedure should ever be carried out for this condition.

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50. Anthony, D. H.: The Fractured Orbit: Diagnosis and Surgical Treatment, Digest Ophth. & Otoloryng. **13**:480-487, 1951.

51. Haemmerli, V.: Injury to the Optic Nerve After Contusion of the Orbital Margin, Ophthalmologica **121**:69-72, 1951.

52. List, C. F.: Progressive Extraperiorbital Hematoma, J. Neurosurg. **8**:340-342, 1951.

53. Favory, A., and Sédan, J.: Ocular Injuries in Boxers, Arch. opht. **11**:429-456, 1951.

54. Wilson, P.: Acute Unilateral Dacryoadenitis: Report of Four Patients, Brit. M. J. **1**:1183-1185, 1951.

55. Sjögren, H., and Kronning, E.: Keratoconjunctivitis Sicca After Partial Extirpation of the Palpebral Lacrimal Gland, Acta ophth. **29**:355-359, 1951.

Irvine and associates [56] state that extirpation of a tumor of the lacrimal gland is the only logical treatment; at the same time, they agree that early removal of the tumor does not prevent recurrences. In their series, the mixed tumor gives recurrences in about 20% of the cases, with a death rate of 32%. The mixed tumors are commoner than the alveolar type. The alveolar type of adenocarcinoma is more malignant because of a tendency to distal metastasis. On the other hand, the mixed tumors eventually recur and become malignant because of invasion of orbital tissue and destruction of orbital bones. Those who prefer to resort to irradiation of lacrimal-gland tumors are advised that, although the mixed tumors are radiosensitive, they require such high doses that surgical removal is preferable. McKinney and Butz [57] state that once metastasis begins the growth appears to take on new impetus and in these foci the tumor is highly anaplastic.

ORBITAL INVOLVEMENT FROM PARANASAL SINUSES

It is the finding of Piquet and Driessens [58] that mucoceles usually originate in the ethmoid cells and may bulge into the frontal, or even the maxillary, sinus, extension taking place by bony absorption. Pressure effects of the mucocele may result in the absorption of bone. The orbital region is the usual site of extension. These authors rarely find a postoperative mucocele, for example, after an operation on the frontal sinus. The contents of the tumor are glary, at times gelatinous, yellow, and sterile, and at times contain red blood cells. When the contents are purulent, the authors suggest that the condition is a transition between suppurative sinusitis and a mucocele. Histologic examination of the wall lining reveals a mucosa consisting of cuboidal or cylindrocuboidal cells, devoid of cilia. Various theories have been suggested to explain the cause of mucoceles. Infections, trauma, retention, cystic degeneration of the mucosa, or congenital anomalies have been thought possible. The authors discuss these possibilities and then express their own view that infection plays an essential part in the causation of mucocele. Depending upon the causal organism, the secretion may be exudative or purulent.

Mucocele of the frontal sinus is of infrequent occurrence, as demonstrated by Kravitz,[59] who found 4 cases of mucocele of the frontal sinus among 327,420 new admissions to the Brooklyn Eye and Ear Hospital. The ocular symptoms in their cases were prominent and consisted of gradually increasing proptosis with displacement of the eye down and out. There was no pain, but there might be fulness or swelling of the forehead above the affected eye, and even swelling of the upper eyelid. Diplopia was not a prominent feature. Impaired vision resulted from pressure upon the eye and optic nerve. Retinal folds, which may be produced by any retrobulbar mass, may appear at the posterior pole. The mucocele has a globular surface, feels slightly cystic, and always appears at the upper and inner end of the orbit. The authors find x-rays useful in diagnosis, although they may be misleading. They believe that surgical treatment only is indicated.

56. Irvine, A. R.; Roberts, W. L., and Soudakoff, P. S.: Tumor of the Lacrimal Gland, Am. J. Ophth. **34**:1511-1519, 1951.

57. McKinney, W. W., and Butz, W. C.: A Mixed Tumor of the Lacrimal Gland with Extensive Metastases, Am. J. Ophth. **34**:1519-1524, 1951.

58. Piquet, J., and Driessens, J.: Pathogenesis of the Paranasal Sinuses, Rev. laryng. **72**:17-31, 1951.

59. Kravitz, D.: Mucocele of the Frontal Sinus, Am. J. Ophth. **34**:985-989, 1951.

PARASITIC CYSTS OF THE ORBIT

Handousa,[60] in reporting on proptosis caused by hydatid disease (echinococcosis), states that the orbit is one of the rarest sites of involvement of this condition. The incidence for the face, orbit, and mouth together is between 0.8 and 2.3% in endemic areas. The cyst walls are formed by the germinal layer, surrounded by a dense fibrous layer. In circumscribed areas the germinal layer sends out processes into the surrounding tissues, which produce metastases along the lymphatics and blood vessels. In a confined bony area the cyst grows, permeates available bony spaces, and destroys the bone. This is termed the osseous cyst. Eosinophilia is not always present, and the reactions to complement-fixation and intradermal tests are not constantly positive. Nine to 12 years is the commonest age for orbital involvement. The author believes that exploration is the most reliable method of diagnosis. He uses x-ray studies after filling with iodized oil and feels that they may often be of diagnostic value. In the three cases he reports, prompt recovery followed surgical removal of the parasite. He suggests leaving a portion of the outer cyst wall in an attempt to avoid endophthalmos.

METHODS OF EXAMINATION OF ORBITAL CONDITIONS

Witmer [61] warns against injection of iodized oil U. S. P. into Tenon's capsule when there is a possibility of double perforation of the eyeball by a foreign body, because of the danger of intraocular seepage of the oily medium. His experience in a case of perforating injury to the globe with the use of iodized oil injected into Tenon's space, for the purpose of more accurate localization of the foreign body by x-rays, was disconcerting in that oily droplets of the iodized oil appeared in the vitreous near the posterior perforation. The eye, however, remained quiet during several months of observation.

Continued interest in orbitotonometry by means of Copper's apparatus has been reported by Hartmann and Van Alphen.[62] They find that the reducibility of the eye in the orbit depends upon the relation between the size of the eye and that of the orbit, the muscular tone, the fluidity of the fat, and the possible presence of a tumor. They are able, by means of the experimental device and the clinical findings, to differentiate two types of curves: a "tumor type" in which the curve is flat (orbital tumors, malignant exophthalmos in Basedow's disease) and an "edematous type," in which the curve is more sloping (orbital inflammations and common exophthalmic goiter). Eleven types of classic exophthalmic goiter were examined according to this method; it was found that in cases of common exophthalmos the reducibility of the eyeball may be complete provided that one waits for a considerable period while applying the pressure. They are of the opinion that the orbitotonometric determinations may prove very useful in the differential diagnosis of orbital tumors.

Roentgen tomography in cases of proptosis, whether unilateral or bilateral, is much used on the Continent and is little appreciated in this country. Fischgold and associates [3c] are of the opinion that examination of both anterior clinoid processes

60. Handousa, A. B.: Proptosis Caused by Hydatid Disease, Brit. J. Ophth. **35**:607-613, 1951.

61. Witmer, R.: Passage of Lipiodol into the Vitreous After Diagnostic Injection into Tenon's Capsule, Ophthalmologica **121**:177, 1951.

62. Hartmann, E., and Van Alphen, G.: Orbitotonometry, Bull. Soc. Ophth., Paris, Supp. 6, 1951.

by frontal tomography is of great value in neuro-ophthalmology. A unilateral lesion of an anterior clinoid process is seen only rarely in cases of intrasellar tumors, e. g., hypophyseal adenoma. On the other hand, roentgen tomography makes unilateral lesions of a clinoid process visible in certain cases of exophthalmos due to tumor and of unilateral lesions of the optic nerve. With the standard x-ray technique, only slight information can be obtained on the nature of the lesion, the accurate localization, and the exact anatomical relations of the orbit, sinus, and intracranial cavity.

Roentgen tomography enables David and associates [3a] accurately to localize orbital tumors and to visualize minor bone erosions in the orbital wall which are practically invisible otherwise. Roentgen tomography of orbital lesions necessitates at least four views in various planes: (1) frontonasal, with the x-ray beam centered under the infraorbital margins; (2) lateral, with the beam centered on the sella turcica; (3) through the optic foramen, and (4) through the nose and chin. With these four x-ray views they are able to identify the orbital margins, the sphenoidal fissures and bones, the ethmoid and frontal sinuses, the optic foramen, the maxillary sinus, the orbital roof, the sella turcica, anterior and posterior clinoid processes, and the sphenoid sinus.

SURGERY OF THE ORBIT

A new operation (transorbital lobotomy), for adventuresome ophthalmic surgeons, is described by Freeman and Williams [63] for the relief of intractable pain in advanced malignant disease. A sharp, slender instrument is inserted into the conjunctival sac 3 cm. from the midline and is driven through the orbital plate 5 cm. into the frontal lobe. Lateral and medial cuts are then made through the white matter. In many operations the orbital plate fractures. There is a resulting communication between the cranial cavity and the orbital tissues, giving rise to swollen lids. No case of rhinorrhea or infection has occurred. The cortical incision severs the thalamofrontal radiation just lateral to the anterior horn of the lateral ventricle, although sometimes penetrating the ventricle and lacerating the caudate nucleus.

The disheartening results in the restoration of a contracted socket by free skin grafts or by buccal mucous membrane are appreciated by all. The contraction of the grafted buccal mucosa in the orbit is considered to be due to lack of sufficient underlying tissue to exert the necessary tension. Dimitriou,[64] recounts his own method of obtaining this tension on the buccal graft by grafting tarsus to the upper and lower conjunctival fornices, the tarsus of the upper and lower lids being split into two sheets, one of which serves for grafting. Foster,[65] in discussing this difficult surgical procedure, states that his best results have been obtained in epithelial socket inlays by tightly filling the socket with cotton-wool soaked in 1/000 acriflavine emulsion after removal of the fibrous tissue and tarsus, if necessary, down to the orbital margin. After this packing is removed, it is covered by a Thiersch graft and replaced. Further pledgets of the same substance are forced into the cavity and under the upper lid to obtain pressure where necessary, and the whole is covered by a pad of the same material without lid suture or tarsorrhaphy.

63. Freeman, W., and Williams, J. M.: Lesions of Transorbital Lobotomy, A. M. A. Arch. Neurol. & Psychiat. **66**:191-198, 1951.

64. Dimitriou, T.: An Improved Technique for Reconstruction of a Contracted Socket, Bull. Soc. hellen. opht. **18**:224-226, 1950.

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Displacement of the trochlea due to osteoma of the orbit may result in serious oculomotor disturbances and present difficulties in its correction. Streiff [66] reports on an orbital osteoma arising at the junction of the frontal and the ethmoid sinus. During the operation the bone to which the trochlea was attached was severed from the orbital wall and the osteoma removed. The trochlea was then sutured to the inner wall of the frontal sinus. After two months the ocular motility was normal.

A frequent complaint of women over 50 is puffiness of the eyelids due to herniation of intraorbital fat. Castanares [67] believes herniation of intraorbital fat is the result of congenital extension of the orbital fat through a defect in the fascia and orbicularis muscle, and that it may be due to a familial tendency to an abnormal regional disposition of fat. There is loss of firmness and elasticity of the skin and of the fascia tarso-orbitalis that lies beneath. Anteriorly, there are three definite and separate pockets of encapsulated fat in the lower eyelid and two similar ones in the upper eyelid. Each one of these lobular groups of fat is well encapsulated, distinct, and independent one from the other. The superior oblique and the inferior oblique muscle further divide these groups of fat in the upper and lower eyelids, respectively. The author finds that each accumulation of fat is well encapsulated by a thin, but firm, connective tissue capsule and that this capsule has to be cut in order to produce protrusion of the fat for its removal; failure to open each capsule will result in incomplete removal.

At operation, Castanares separates the orbicularis fibers by blunt dissection but none are excised. The removal of the herniated fat should be started first through a stab opening in the lateral aspect of the lower lid. The other pockets are then reached by incising the capsule with scissors, and the fat is removed through the lower incision line and by skin resection of the lids. As much fat is removed as is thought to be excessive, which is usually that portion presenting above the glistening white periosteum of the orbital margins. The tarso-orbital fascia should be cut along the separated fibers of the orbicularis muscle. Castanares finds it difficult and unnecessary to suture together the margins of the ruptured fascia after the extirpation of fat.

Suarez Villafranco [68] uses free grafts from the forearm for filling defects, cicatricial ectropion, restoration of the orbital or conjunctival cavity, and reconstruction of the lower lid. He describes an appliance which he designed for stretching the skin of the forearm and facilitating the excision of the graft and a forceps for holding the graft and tying sutures.

Cases of acute orbital cellulitis which threaten vision owing to orbital pressure do not always permit incision and drainage. Delaney and Oliver [69] solved the problem in one of their patients by a transmaxillary approach through the canine fossa. The roof of the sinus was removed, and when the fascia had been incised, the pressure was released.

66. Streiff, E. B.: Recession of the Insertion: Displacement of the Base of the Trochlea in a Case of Orbital Osteoma, Ophthalmologica **121**:114-117, 1951.

67. Castanares, S.: Blepharoplasty for Herniated Intraorbital Fat: Anatomical Basis for New Approach, Plast. & Reconstruct. Surg. **8**:46-58, 1951.

68. Suarez Villafranco, M. R.: Plastic Surgery of the Lids with Free Grafts, Arch. Soc. oftal. hispano-am. **10**:851-860, 1950.

69. Delaney, A. J., and Oliver, S. H.: Orbital Decompression, Transmaxillary Approach, U. S. Armed Forces M. J. **2**:1079-1084, 1951.

Postherpetic pain, unrelieved by evulsion of the left supraorbital nerve, irradiation of the left trigeminal ganglion, left retrogasserian neurectomy, left supraorbital gyrectomy, and left cervical sympathectomy, responded normally to right supraorbital gyrectomy, as reported by Bonner and his associates.[70]

ORBITAL IMPLANTS

Time is gradually accumulating sufficient to permit more adequate evaluation of the long-term results of integrated implants. In spite of annoying, but variable, secretion in all cases, and in spite of other complications that result in spontaneous extrusion in a number of cases, or the necessity of its removal in others, Drucker and associates[71] find the remark that "about 75% of the patients with integrated implants are extremely happy over the appearance and movement of the prothesis" is perfectly true. The other 25% of the patients can, however, be most disturbing to themselves and to their surgeons. These authors believe that the idea of integrated implants is sound and that further work along this line should be continued. In their opinion, the problems of the complications are not insurmountable, but at present the surgeon must curb his enthusiasm and present to the patient a realistic and valid picture of what may be ahead of him in the way of complications and possibilities. Kennedy and Shipman,[72] however, after following 27 integrated implants, note that 10 (37%) have been extruded. They conclude from their experience that they are not justified in continuing use of the integrated implant.

Stone[73] presents a follow-up report on 112 cases of integrated implants; he finds that the principal complications are secretion, granulation tissue or polyps at the edge of the conjunctiva, exposure of the meshwork, and operative difficulties, with secondary or delayed implants. Forty-one patients showed moderate to severe secretion, and these patients were instructed to irrigate the socket thoroughly every morning with a saline solution, followed by 10 dropperfuls of 1 : 1,000 benzalkonuim chloride. An antibiotic ointment is introduced into the socket at night. Formation of granulation tissue and polyps is attributed to the interposition of subconjunctival tissue beneath the conjunctival edge or the inadvertent picking up Tenon's capsule instead of suturing the conjunctival edge to the mesh work. The author suggests careful dissections of the conjunctiva and the insertion of a purse-string suture at the beginning of operation in order that tissues may not be confused as the operation is concluded. He suggests removal of the granulations and polyps and cauterization of the base of their dissection from beneath the conjunctiva and resuturing of the conjunctiva to the implant. Exposure of the meshwork is attributed to defects in manufacture of the implant. His experience with the results of secondary implantation is not encouraging. He attributes his poor results chiefly to the difficulties in

70. Bonner, F. J.; Cobb, S., and Sweet, W. H.: Orbital Gyrectomy for Intractable Pain, A. M. A. Arch. Neurol. & Psychiat. **66**:238-240, 1951.

71. Drucker, A. P.; Kreft, W. W.; Pearlman, M. D.; Rosenau, J. A., and Snip, R. T.: Integrated and Buried Implants, Am. J. Ophth. **34**:1483-1498, 1951.

72. Kennedy, P., and Shipman, J. S.: Exposed Implants: A Follow-Up Report, A. M. A. Arch. Ophth. **46**:460-461, 1951.

73. Stone, W., Jr.: Movable Postenucleation Implants: Complications and Their Solution, J. A. M. A. **145**:371-375, 1951.

technique or in identification of the retracted and cicatrized muscles and to the changes in the anatomical structure of the muscles and the socket following the enucleation.

Continued enthusiam in the development of integrated implants in many quarters is evidenced by reports during the past year of the application of new principles in their use. Culler [74] presents a new modification of a partly buried plastic implant having a projecting anterior neck 11.5 mm. in diameter, which is covered with tantalum mesh. The neck is used for positioning of the rectus tenddons. Culler believes that the four rectus muscles and, if possible, the two oblique muscles should be attached to the mobile stump or implant, so that they will not atrophy. Of the 23 implants used, he finds that movements are fairly normal in all directions except temporally, where there is some drag in extreme rotations.

Young [75] describes the development of a plastic implant for the eviscerated globe. The implant is fixed with tantalum wires passing through the sclera to insure the implant healing in the proper position. A peg on the anterior surface at operation is passed through a hole in the cornea. This peg acts as an obturator on which the prosthesis rests. After evisceration of the contents, the tantalum wires are passed through the sclera and through the holes drilled in the implant, and the peg projects through a hole made in the cornea. The scleral wound is closed, and the entire contents are covered with conjunctival and episcleral tissues. The wound is closed with interrupted black silk sutures. Daily dressings are advised. An advantage claimed by the author for this implant is excellent mobility in all directions.

RETROBULBAR INJECTIONS

Local and systemic administration of cortisone in ocular disease has already demonstrated its effectiveness in many conditions and is yet to be proved of value in others. Leopold and his co-workers [76] found that posterior uveitis was little affected by subconjunctival or retrobulbar administration (50 mg. with 0.5 ml. of 4% procaine hydrochloride) but two patients treated systemically (100 mg. every 8 hours for three days, every 12 hours for two days, and daily thereafter) were greatly benefited. The authors found that macular degeneration and retrobulbar neuritis were unaffected by either systemic or retrobulbar administration. They found that reactions to the drug were remarkable only after retrobulbar injections, when one should be prepared for unusual intense reactions of edema in occasional cases.

With the addition of hyaluronidase, in doses of 0.33 mg. per milliliter, to the anesthetic (cocaine, tutocain®) a more profound and prolonged anesthesia, followed by rapid disappearance of the edema resulting from the fluid which was administered, was observed by Anastasi [77] in 150 cases of infiltration anesthesia (50 operations on the eyelid, 50 resections of the lacrimal sac, 25 inductions of akinesia, and

74. Culler, A. M.: Enucleation and Cosmetic Rehabilitation: Criteria for Evaluation of Current Procedures, A. M. A. Arch. Ophth. **45**:445-457, 1951.

75. Young, J. H.: A New Ocular Prosthetic Aid: The Intra-Ocular Implant, Brit. J. Ophth. **35**:623-627, 1951.

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77. Anastasi, G.: The Additional Use of Hyaluronidase in Infiltration Anesthesia in Ocular Surgery, Silicia sanit. **3**:27-30, 1950.

25 anesthesias of the ciliary ganglion). He found that retrobulbar injections produced a striking decrease in intraocular pressure, facilitating total extractions of cataract and iridectomy for glaucoma.

When administering curare intravenously for akinesia, Barraquer [78] uses no retrobulbar or facial-nerve injections. The dose of curare depends on the weight of the patient—for a very heavy man he advises 10 mg.; for a normally developed patient about 7.5 mg., and for a very thin person, 5 mg. The author claims that there are no risks if his technique is followed. The antidote is neostigmine, and curare should not be used in cases of myasthenia.

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Society Transactions

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A. G. DeVoe, M.D., Secretary

Regular Meeting, March 17, 1952

Pathological Report of Enucleation of Globe Four Days After Cataract Extraction. Dr. Gerald B. Kara.

The case of an eye removed four days after cataract extraction because of the observation of malignant intraocular tumor was reported. The operative procedure consisted in knife section enlarged with scissors, complete iridectomy, and intracapsular extraction with three post-placed chromic absorbable surgical (gut) sutures. A fornix-based conjunctival flap was used. In general, the pathological findings in the healing wound were comparable to those demonstrated in animal eyes by other authors. Of importance were areas of necrosis and epithelization around the chromic absorbable surgical sutures.

DISCUSSION

Dr. Samuel Gartner: Few opportunities have been presented for early study of eyes that have been operated on for cataract with sutures. This case of Dr. Kara's is the earliest one in the American literature. Those who use absorbable surgical (gut) sutures should be interested in the amount of reaction around the sutures, which appears to be much more than in the cases in which nonabsorbable (silk) sutures have been used. The epithelization around the sutures is something to give us pause.

Orthoptic and Surgical Treatment of Intermittent Exotropia. Dr. Abraham Schlossman, Dorothy Parkhill, and Leta Counihan.

The results of orthoptic training in 38 patients with intermittent exotropia were summarized according to the following criteria of improvement: (1) conversion of intermittent exotropia to a constant exophoria; (2) the development of the three grades of fusion, with the use of slides with macular controls on the troposcope, in cases in which there was no fusion at first, or only momentary first- or second-grade fusion; (3) improvement of the amplitude of fusion, especially convergence, with the use of macular controls.

Fifteen patients showed pronounced improvement with orthoptic exercises alone. Three patients who had surgical procedures needed orthoptic training before they acquired constant exophoria. Of seven patients who showed only moderate improvement, three originally had a constant exotropia at distance but developed intermittent exotropia at 6 meters. Two showed rather marked improvement but retrogressed within three months after the training had been discontinued. Eleven patients showed no improvement at all after apparently adequate orthoptic training.

It was suggested that the terms "convergence insufficiency" and "divergence excess" be dropped in referring to cases of intermittent exotropia because constant and intermittent exotropia and significant exophoria are considered different degrees of the same condition, and from a hereditary point of view divergent strabismus is the same whether it is intermittent or constant.

Thus, it was shown that in certain cases orthoptic training is actually the treatment of choice. Even when orthoptic training fails, the various examinations by an orthoptic technician will enable a better evaluation of the status of the patient's

strabismus, so that the surgeon will be able to plan his procedures with greater confidence. It is suggested that any patient with intermittent exotropia be given a trial period of orthoptic training prior to operation.

Relation of Ocular Changes to Disorders of Thyroid Function. Dr. Lawrence W. Sloan.

The author stated that serious ocular changes usually occur in persons with a diffusely hyperplastic toxic thyroid and rarely, if ever, in persons with toxic nodular goiter. The ocular disorders fall roughly into two categories: simple disorders of the opening and closing mechanism of the lids, in which the problem is largely cosmetic and seldom serious, and disorders which are serious because of infiltration of the orbital contents with edema and cells and which ultimately may result in fibrous fixation of the globe. In a study of 615 cases of toxic thyroid made five years or longer after operation, the incidence of severe ocular changes was between 0.5 and 1%. In attempting to anticipate those cases of thyroid disease in which serious ocular changes may develop, the following points have seemed important: (1) The majority of the patients are in the older age group, from 39 to 55 years of age; (2) these changes develop in a higher proportion of men than women; (3) thyroid function at the time of the initial changes is usually only mildly toxic, or may be even normal, so that ocular signs develop out of proportion to the clinical evidence of hyperthyroidism; (4) significant early local signs and symptoms are lid fulness, lacrimation, a sense of fulness or pressure in the eye, and, at times, diplopia.

Any of these features individually may be misleading, but the occurrence of the changes in combinations may indicate a potential "malignant exophthalmos." Treatment remains unsatisfactory, but the process is usually self-limited. It is the belief of thyroid clinicians that the serious ocular changes are occurring less frequently because of careful management and the clinician's awareness that ocular complications can occur.

Ophthalmic Surgery in the Ocular Complications of Thyroid Pathology. Dr. Edmund B. Spaeth, Philadelphia.

In this presentation, attention was called to the four surgical procedures which are available and which are a necessary part of the treatment of exophthalmos. Regardless of the exact etiological agent involved, such treatment has as its purpose many demands other than the relief of the patient from stationary or symptomatic exophthalmos. Some of the procedures may be not only eye-saving but even life-saving.

Surgical correction of the oculomotor paralyses, recession of the levator tendon for lagophthalmos, angle tarsorrhaphy, and the necessary orbital decompression were the four basic surgical procedures discussed. Since the technique of these various operations is well known, indications were especially stressed.

The paper in its entirety will be published elsewhere.

DISCUSSION OF PAPERS BY DRS. SLOAN AND SPAETH

Dr. Wendell L. Hughes, Hempstead, N. Y.: I wish Dr. Sloan would discuss the question of irradiation of the pituitary gland in an effort to reduce the activity of the anterior lobe of the pituitary and its possible effect on exophthalmos, especially the thyrotropic type.

The differential diagnosis based on the etiologic factor in exophthalmos is sometimes extremely difficult. In any case in which the edema is increasing sufficiently to endanger the eye from corneal exposure local protective measures would seem necessary. Occasionally in mild cases a moist-chamber arrangement on a pair of glasses will lessen evaporation from the front of the eye and relieve some of the annoying symptoms.

I am glad that Dr. Sloan mentioned the unilateral cases. They always provide a special problem in diagnosis and frequently lead to errors in therapy. The exophthalmos remains stationary for years, and moderate in amount with little, if any, demonstrable endocrine dysfunction. Dr. Sloan mentioned several of his cases in which the exophthalmos remained stationary for several years and then regressed, and others in which the exophthalmos became pronounced in the fellow eye later.

Dr. Spaeth mentioned surgical procedures on the extraocular muscles. I wonder whether he has found increased edematous reaction after operation in the cases of thyrotropic paralysis, when the muscles are sometimes swollen to three times their normal size, and whether he uses a pressure dressing to combat this edema. I should also like to ask whether he keeps a pressure dressing on, and, if so, for how long, after recession of the levator muscle in cases of thyrotoxicosis. I should also like to ask about the technique of tarsorrhaphy in the cases of thyrotropic exophthalmos in which the lids are very tight, owing to the increase in volume of orbital tissue. Does he have any particular directions in regard to the loosening of the lids? Does he think that it is necessary to incise the tarso-orbital fascia at the orbital margin in order that the lids may be brought together to produce the tarsorrhaphy? Or does he feel that the marginal deepithelization of the lids and the ordinary type of tarsorrhaphy, as described by Wheeler, is sufficient? I know I have had failures with this type of tarsorrhaphy in these desperate cases.

Dr. Spaeth hinted at the dangers of irradiation of the orbit in cases of thyrotropic exophthalmos, dangers which I believe should be emphasized.

The management of these cases always requires the greatest diagnostic acumen and surgical judgment. Dr. Spaeth's paper is helpful in the clarification of many aspects of the management of these cases.

Dr. Isadore Givner: I should like to call attention to a test which should be done in cases of unilateral exophthalmos in deciding whether the condition is due to the thyroid or to a tumor of the orbit—that is pupillography. In cases in which a thyroid dyscrasia is present one will find a redilation block which is indicative of central sympathetic disturbance. This will point to the thyroid, rather than to orbital tumor.

Can Dr. Sloan say whether any of the other functions of the pituitary were influenced adversely by radiation in those cases of thyrotropic exophthalmos in which it was used?

Dr. Spaeth mentioned that retinal detachment was sometimes associated with thyrotropic exophthalmos. I have never seen or heard of that complication, and I should appreciate it if he would elaborate on that finding.

Dr. David Wexler: I should like to ask Dr. Spaeth whether he has ever combined recession of the levator with tarsorrhaphy. I recall that Dr. Goldstein, at Dr. Wheeler's suggestion, occasionally combined recession of the levator with tarsorrhaphy and found it very effective in management of the progressive malignant type of exophthalmos.

Dr. Lawrence W. Sloan: I should like to repeat that the mechanism of production of these ocular changes is not a clear-cut cause-and-effect relation between thyroid function and function of the anterior lobe of the pituitary. It is not as simple as that—too many clinical situations commonly seen remain unexplained by that oversimplified explanation.

My experience with irradiation of the pituitary gland for these severe ocular changes has been limited. Several years ago, with the assistance of Dr. Maurice Lenz, I tried it on a few patients. We irradiated the orbits also, but in neither case were we sufficiently impressed with the results to continue using this method. There has been a good deal written in the recent medical literature about the use of x-ray therapy to the pituitary gland in cases of severe exophthalmos, but of this, as of any reports of therapy of this condition, one must be severely critical, for, as I tried to explain, the process is self-limited. One who is unfamiliar with the natural

history of the disease may be inclined to ascribe improvement to the therapy, when, in fact, it might have occurred anyway. It is the relatively rapid development of severe ocular changes following thyroidectomy in so many of the cases reported which has led me to the strong conviction that there is a close relation between the two. In addition, there are theoretical reasons for doubting that x-ray therapy will be of value, not the least being that the thyrotropic mechanism has not been fully established as the cause. In addition, there are doubts about the efficacy of treating the anterior lobe of the pituitary with sufficient radiation to depress its function selectively, particularly without damage to other functions or structures in that area.

A number of practical and theoretical factors seem, therefore, to make it unlikely that one should expect x-ray therapy to have any effect on this process. The patients I have seen who have been so treated showed no clinical changes which could be ascribed to alterations of other pituitary functions.

Dr. Edmund B. Spaeth, Philadelphia: Among the various questions which were asked was one regarding surgical procedures on the extraocular muscles: I called attention to that by indirection, rather than by affirmation, when I stated that one cannot operate on the conjugate yoked muscles in the correction of these situations; one must operate on the paralyzed muscle because the muscle degeneration is so definite, so pronounced, and so damaging that all one can do is to change the faulty position of the eyeball a little less than it was before the operation. Dr. Hughes is correct when he states that these muscle fibers are twice, or three or four times as thick as normal and are swollen and edematous. Fortunately, however, the tendons are unchanged, so that one can perform the surgical correction with the oculomotor tendon. Surgery on the conjugate yoked muscle would be quite hopeless.

Dr. Hughes asked what I do in orbital decompression with tight lids. I have found it expedient—in fact, necessary—several times to combine both orbital decompression and tarsorrhaphy with the recession. I have not combined a levator recession with a decompression, or a tarsorrhaphy with a decompression; but I think it is quite proper when it is necessary.

I have not used pressure dressings at any time in these cases, and I do not believe they would be of any value.

The last question was that of retinal detachment in thyrotropic exophthalmos. It was then that I criticized the use of the term "papilledema." I believe that this so-called papilledema is an edema of the retina proper and is not due to intracranial pressure. In two instances I have seen edema of the peripapillary portion of the retina advance to such a stage that a true retinal separation occurred, with degeneration of the retina and with an enormous stationary blind spot; so retinal separation as such does occur.

News and Comment

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

Central Illinois Society of Ophthalmology and Otolaryngology.—The next meeting of the Central Illinois Society of Ophthalmology and Otolaryngology will be held at the Abraham Lincoln Hotel in Springfield, Ill., on Sept. 12, 13, and 14. The guest speakers will be Dr. Paul A. Chandler, of Boston, and Dr. Thomas C. Galloway, of Evanston, Ill.

American Ophthalmological Society.—At the 88th Annual Meeting of the American Ophthalmological Society, the following officers were elected: president, Dr. Conrad Berens; vice-president, Dr. William L. Benedict; secretary-treasurer, Dr. Maynard C. Wheeler, and editor, Dr. Gordon M. Bruce.

Seventeenth International Congress of Ophthalmology.—The 17th International Congress of Ophthalmology will take place at the Waldorf-Astoria Hotel, in New York, the week beginning Sept. 12, 1954, marking 97 years after the meeting of the 1st International Congress, held in Brussels, in 1857. This will be the second time in 78 years that the Congress has been held in the United States, the previous meeting being the 5th Congress, held in New York, in 1876. The last meeting was held in London, in 1950.

The International Congresses take place every four years except for interruptions caused by wars. They are conducted under the authority of the International Federation of Ophthalmological Societies, one of the oldest of all international organizations. The broad aim of the Federation, which is composed of delegates sent by ophthalmological societies of many countries, is to promote the science of ophthalmology throughout the world.

Dr. Bernard Samuels, of New York, will serve as president of the 17th International Congress, with Dr. John H. Dunnington, also of New York, as vice-president, and Dr. William L. Benedict of Rochester, Minn., as secretary-general.

The invitation to the Congress to meet in this country was the joint action of four national groups: the American Ophthalmological Society, the Section on Ophthalmology of the American Medical Association, the Association for Research in Ophthalmology, Inc., and the American Academy of Ophthalmology and Otolaryngology.

It is tentatively planned that the annual meeting of the American Academy of Ophthalmology and Otolaryngology will be held at the Waldorf-Astoria Hotel the week following the 17th International Congress.

The International Council has met recently in Oxford and has selected the subjects which will be discussed at the Congress, namely, Primary Glaucoma and Etiology of Uveitis. On each of these subjects there will be three main papers.

Primary Glaucoma:

1. Etiology and General Considerations. Dr. Derrick Vail, Chicago
2. Medical Therapy. Dr. R. Thiel, Frankfurt am Main, Germany
3. Surgical Treatment. Dr. Gabriel Sourdille, Nantes, France

Etiology of Uveitis:

1. General Considerations. Dr. Alan C. Woods, Baltimore
2. Allergic Factors. Dr. Norman Ashton, London, England
3. Virus Factors. Dr. Vittoriano Cavara, Rome, Italy

Those who wish to present dissertations or to participate in discussions should communicate with the secretary-general. English, French, and Spanish are the official languages of the Congress, but any language may be used. Communications should not be longer than 2,500 words and will be read in abridged form. On submission, each paper should be accompanied by a résumé of about 250 words in each of the three official languages. Papers published prior to the meeting of the Congress are not acceptable. The publication committee reserves right of rejection.

Scientific and clinical demonstrations will be scheduled, and there will be scientific and industrial exhibitions.

It is hoped that this meeting will be as stimulating as previous Congresses. Delegates from more than 50 countries are expected. This will give a rare opportunity for making of new acquaintances and the renewing of old ones.

Further information will be published from time to time. All correspondence should be directed to Dr. William L. Benedict, Secretary-General, 100 First Ave. Bldg., Rochester, Minn. Offers of papers and scientific exhibits are now being received at his office.

Indianapolis Ophthalmological and Oto-Laryngological Society.—The officers of the Indianapolis Ophthalmological and Oto-Laryngological Society for 1951-1952 are as follows: Marlow W. Manion, M.D., president; Robert W. Dearmin, M.D., vice-president; Lewis E. Morrison, M.D., secretary-treasurer.

Pan-American Association of Ophthalmology.—The Pan-American Association of Ophthalmology has announced that the officers of the Fifth Pan-American Congress of Ophthalmology, to be held in Santiago, Chile, in February, 1956, will be Dr. Cristobal Espildora, president; Dr. Santiago Barrenechea, vice-president; Dr. Rene Contardo, secretary-general, and Dr. Abraham Schweitzer, treasurer.

PERSONAL NEWS

1952 Medal in Ophthalmology to Dr. Bedell.—At the One-Hundred First Annual Session of the American Medical Association, held in Chicago June 9 to 13, the Section on Ophthalmology presented the Medal for outstanding contribution to ophthalmology in 1952 to Arthur J. Bedell, M.D.

Dr. William E. Krewson III's Appointment.—Dr. William E. Krewson III has recently been appointed Director of the Departments of Ocular Motility and Perimetry at the Wills Hospital, Philadelphia.

CORRECTION

In the review of the book "Lehrbuch der Augenheilkunde" in the April issue, page 550, it was incorrectly stated that the price is $6.89. The actual price of this work is $12.

Books

Le traitement du glaucoma infantile. By Algan Bernard, Nancy. Pp. 209, Imprimerie Georges Thomas, Angle des rues de Solignac et Henri-Lepage, 1951.

This monograph presents a rather exhaustive review of the treatment of congenital glaucoma. Medical therapy was of little value, and in nearly all cases surgical intervention was eventually required.

Paracentesis, posterior sclerectomy, anterior sclerectomy, extraction of the crystalline lens, and iridectomy are discussed, but are dismissed from consideration as being of only transient effectiveness or so fraught with complications as to be impractical. The author is particularly fond of cyclodiathermy as done by the Vogt method. He reports 26 cases, with 23 successful results, but no patient had been observed over one year. He had no case in which disorganization of the angle or opacity of the cornea occurred. Nor did he encounter hemorrhage of the iris, lens opacities, or retinal hemorrhage. The method of Weekers, in his opinion, is too new for evaluation.

In attempting to construct a therapeutic program for cases of congenital glaucoma, the author divides the disease into four stages: In the first stage, in which the eye presents little or no damage, goniotomy is the treatment of choice. However, iridencleisis, trephination, or cyclodiathermy may be used effectively. In the second stage, when the eye begins to enlarge, goniotomy may be used if the angle can be visualized, but is risky if the angle cannot be seen. In such a case, fistulizing operations are ideal. The author has also used cyclodiathermy as a primary procedure. In the third stage, in which the globe is greatly enlarged and the canal of Schlemm is obliterated, goniotomy cannot be used. Fistulizing operations result in loss of vitreous, hemorrhage, and retinal detachment. Iridencleisis and cyclodiathermy are the only methods acceptable. In the fourth stage, it is a question of enucleation or of cyclodiathermy. The author believes that cyclodiathermy is useful in such late cases.

This monograph presents an excellent view of the treatment of infantile glaucoma and as such is a worth-while addition to any ophthalmic library.

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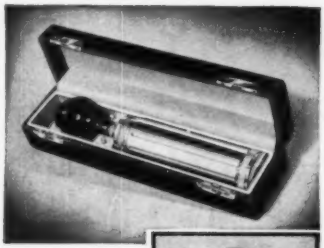

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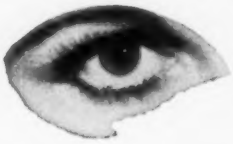

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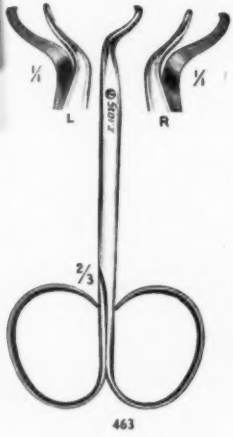

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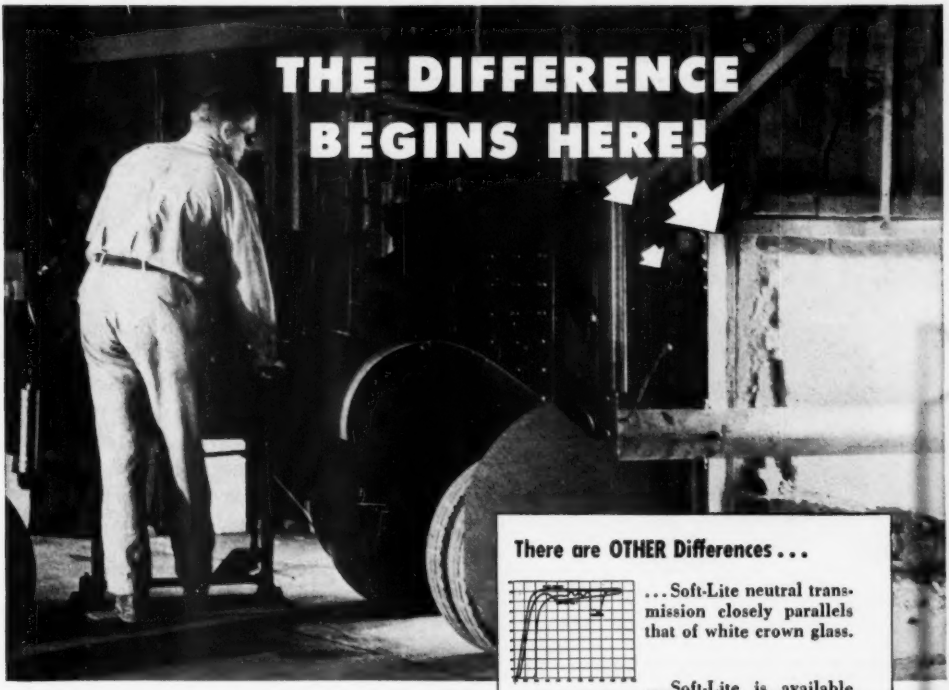

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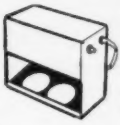

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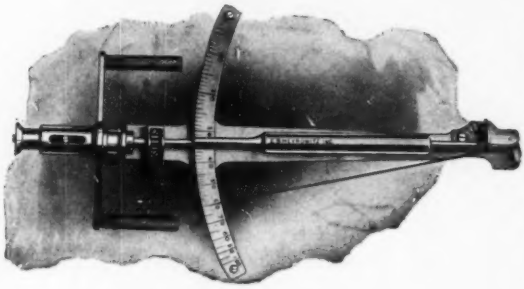

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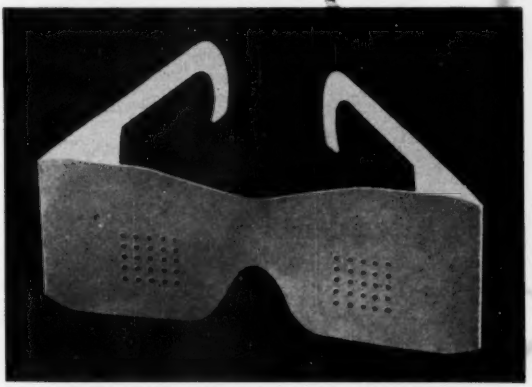

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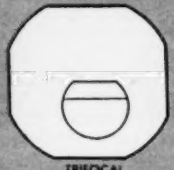
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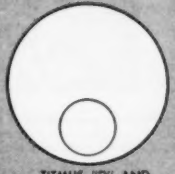
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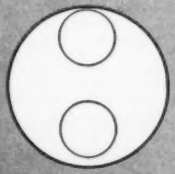
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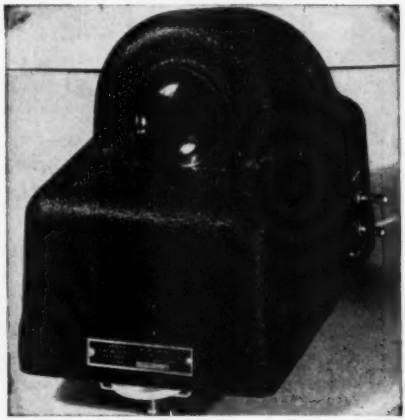

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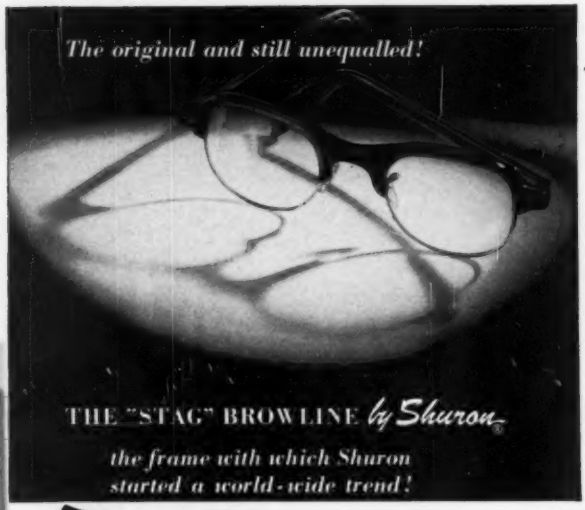

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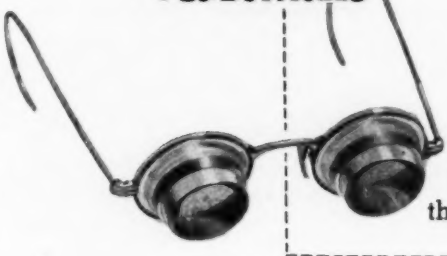

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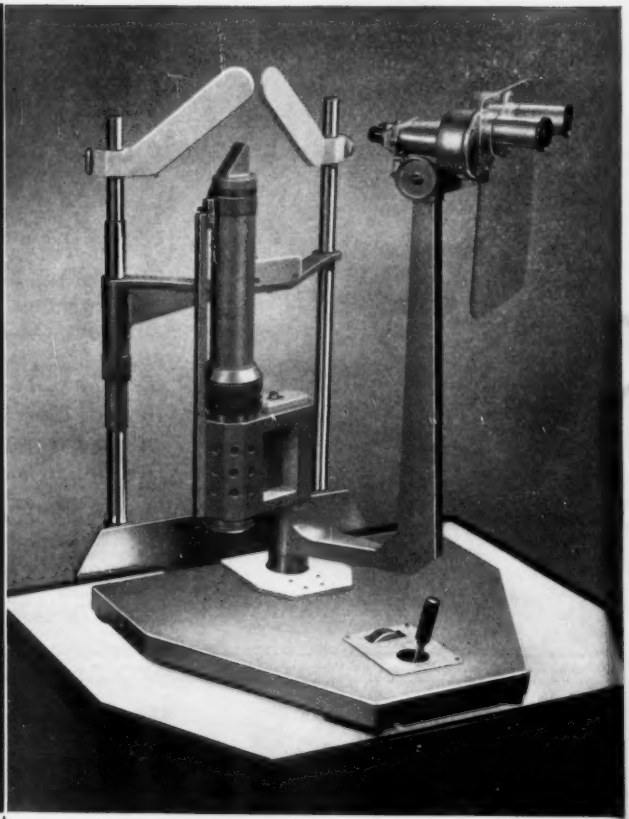

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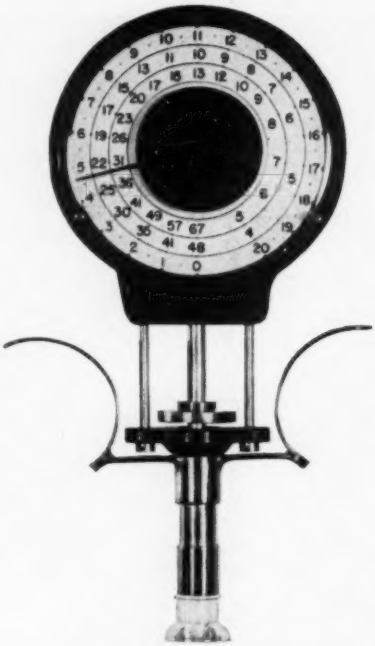

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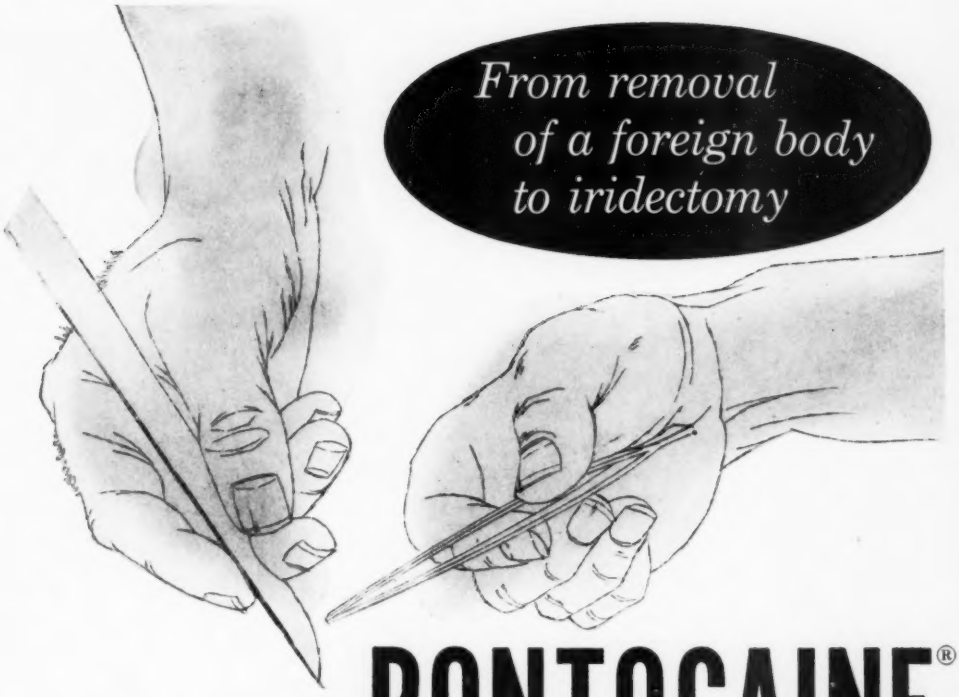

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